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NEUROPATHOLOGICAL AND GENETIC DETERMINANTS OF DEMENTIA:
A PROSPECTIVE AND POPULATION-BASED STUDY ON VERY ELDERLY
FINNS

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Academic Dissertation

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To my family

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following articles, referred to in the text by their Roman numerals

- I Tanskanen, M., Makela, M., Myllykangas, L., Notkola, I.L., Polvikoski, T., Sulkava, R., Kalimo, H. & Paetau, A. 2012, "Prevalence and severity of cerebral amyloid angiopathy: a population-based study on very elderly Finns (Vantaa 85+)", *Neuropathology and applied neurobiology*, vol. 38, no. 4, pp. 329-336.

- II Makela, M., Paetau, A., Polvikoski, T., Myllykangas, L. & Tanskanen, M. 2016, "Capillary amyloid-beta protein deposition in a population-based study (Vantaa 85+)", *Journal of Alzheimer's disease*, vol. 49, no. 1, pp. 149-157.

- III Tanskanen, M., Makela, M., Notkola, I.L., Myllykangas, L., Rastas, S., Oinas, M., Lindsberg, P.J., Polvikoski, T., Tienari, P.J. & Paetau, A. 2017, "Population-based analysis of pathological correlates of dementia in the oldest old", *Annals of clinical and translational neurology*, vol. 4, no. 3, pp. 154-165.

- IV Makela, M., Kaivola, K., Valori, M., Paetau, A., Polvikoski, T., Singleton, A.B., Traynor, B.J., Stone, D.J., Peuralinna, T., Tienari, P.J., Tanskanen, M. & Myllykangas, L. 2018, "Alzheimer risk loci and associated neuropathology in a population-based study (Vantaa 85+)", *Neurology. Genetics*, vol. 4, no. 1, pp. e211.

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ABBREVIATIONS

aa	Amino acids
A β	Amyloid beta protein
ABCA7	ATP-Binding cassette, sub-family A, member 7
ABCG1	ATP- Binding cassette, sub-family G, member 1
AD	Alzheimer's disease
ADRP	Alzheimer's-disease-related pathology
APOE	Apolipoprotein E
APP	Amyloid precursor protein
BBB	Blood-brain barrier
BIN1	Binding Integrator 1
CAA	Cerebral amyloid angiopathy
capA β	Capillary amyloid β -protein
CASS4	Cas scaffolding protein family member 4
CD2AP	Phosphatidylinositol binding clathrin assembly protein
CD33	CD33 molecule
CERAD	Consortium to establish a registry of Alzheimer's disease
CELF1	CUG RNA-binding protein and embryonal lethal abnormal vision-type RNA-binding protein 3-like factor 1
chr	Chromosome
CLF1	CUGBP, Elav-like family member 1
CLU	Clusterin
CR1	Complement component (3b/4b) receptor 1
CSF	Cerebrospinal fluid

CT	Computerized tomography
DLB	Dementia with Lewy bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPHA1	Epherin receptor A1
EXOC3L2	Exocyst complex component 3-like 2
FAD	Familial Alzheimer's disease
FERMT2	Fermitin family member 2
FET	Fused in sarcoma - Ewing's sarcoma - TATA-binding protein-associated factor 15
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
fvAD	frontal variant of Alzheimer's disease
GAB2	GRB2-associated-binding protein 2
GALNT7	GalNAc transferase 7
GWAS	Genome-wide association study
HLADRB1/5	Major histocompatibility complex, class II, DR beta1/5
HP	Hyperphosphorylated
ICH	Intracerebral haemorrhage
IHC	Immunohistochemistry
ISF	Interstitial fluid
LB	Lewy-body
INPP5	Inositol polyphosphate-5-phosphatase
LRP1	Low density lipoprotein receptor-related protein 1
LOAD	Late onset Alzheimer's disease
MCI	Mild cognitive impairment

MEF2C	Myocyte enhancer factor 2C
MI	Micro-infarction
MRI	Magnetic Resonance Imaging
MS4A	Membrane-Spanning 4-domains, subfamily A
NFT	Neurofibrillary tangles
NFTD	Neurofibrillary tangle-predominant dementia
NIA-RI	National Institute on Aging and Reagan Institute
NME8	NME/NM23 family member 8
NP	Neuritic plaques
NT	Neuropil thread
PART	Primary age-related tauopathy
PCA	Posterior cortical atrophy
PCR	Polymerase chain reaction
PET	Positron emission tomography
PICALM	Phosphatidylinositol binding clathrin assembly protein
PS1	PreSenilin 1
PTK2B	Protein tyrosine kinase 2 beta
SLC24A	Solute carrier family 24, member 4
SNP	Single nucleotide polymorphism
SORL1	Sortilin-related receptor 1
TDP	TAR DNA-binding protein-43
TREM2	Triggering receptor expressed on myeloid cells 2
TRIP4	Thyroid hormone receptor Interactor 4
VaD	Vascular dementia

VCI	Vascular cognitive impairment
ZCWPW1	Zing-finger, CW type with PWWp domain 1

ABSTRACT

The number of individuals suffering from dementia increases as the population ages. Alzheimer's disease (AD) is the most common type of dementia, neuropathologically characterized by neuritic plaques (NP) and neurofibrillary tangles (NFT). Cerebral amyloid angiopathy (CAA, deposition of amyloid β (A β) in the cerebral vessels) is often found in AD, but its role in dementia has been unclear. Recent genome-wide association studies have revealed approximately 30 AD risk loci.

The aim of this thesis was to assess the neuropathological and genetic risk factors of dementia in a population-based cohort of very elderly (Vantaa 85+). Of the 601 subjects aged >85 years and living in Vantaa in 1991, 300 (mean age-at-death 92 ± 3.7 years) were examined neuropathologically and 278 genetically. The diagnosis of clinical dementia was based on the DSM III-R criteria. In addition to AD-related neuropathology, Lewy body (LB)-related pathology and several vascular pathologies were analysed. Genetic analyses were based on genome wide approaches.

65% of the study subjects were demented. Except for one subject, at least one type of neuropathology was found in every individual. Presence of at least two of these pathologies almost doubled the risk of dementia. Severe NFT-pathology was the most common finding, and associated most strongly with dementia. LB-related pathology and small cortical infarcts in the anterior brain regions were also independent contributors of dementia. In addition, severe CAA in the frontal lobe was nearly significantly associated with dementia.

CAA was found in nearly 70% of the subjects, but it was mostly mild, found approximately in 1% of the brain vessels. The parietal and frontal lobes were affected most often. In this study, the presence of capillary A β (capA β) was for the first time investigated in a population-based setting and was found in 28.6% of the subjects. Interestingly, every subject with severe capA β deposition in multiple brain areas was demented.

Analyses of 24 of previously known genetic risk loci for AD revealed associations with various types of AD neuropathologies (NP, NFT, CAA, capA β). Genetic risk factors for capA β were identified for the first time.

This study confirmed in a population-based setting previously described findings on neuropathological and genetic factors of dementia. The very high frequency of CAA and the

association of capA β with dementia were shown. Genetic associations of capA β were reported for the first time.

Key words: dementia, Alzheimer's disease, cerebral amyloid angiopathy, capillary amyloid angiopathy, population-based study

1. INTRODUCTION

Age at death is increasing worldwide, especially in developed countries. Simultaneously, the prevalence of old age-associated dementia disorders is increasing, the prevalence being approximately 4% in subjects younger than 75 years, 10-25% in those aged 75 to 85 years, and 40% in subjects aged over 85 years (Lobo *et al.* 2000). At the end of 2015, approximately 120 000 of the 230 741 individuals over 75 years in Finland were suffering from dementia (Statistics Finland, National Institute of Health and Welfare, Finland). In 2015, dementia disorders were the third most common cause of death in Finland, with more than 8 500 deaths, mostly of women, at the average age of 88 years (Statistics Finland).

The clinical presentation of dementia disorders varies. Sporadic, late onset Alzheimer's disease (LOAD) has been considered to be the most common form of dementia, followed by vascular (VaD), Lewy body (DLB), and frontotemporal dementia (FTD). However, recent studies suggest that purely AD, DLB or VaD types of dementia in the elderly may be less common than originally thought (Kalaria *et al.* 2016, Kawas *et al.* 2015, James *et al.* 2012, Savva *et al.* 2009), and that especially in the elderly, mixed pathologies are suggested as the cause of dementia and cognitive decline (Jellinger 2004). Thus, the clinical diagnosis of dementia or its subtype may be challenging. Although there are no specific therapies available for the specific subtypes of dementia yet, their correct recognition is likely to be essential for the development of treatment and medication in the future. Interestingly, elderly subjects may have abundant degenerative brain pathology ADRP lesions, including neuritic plaques, neurofibrillary tangles (NFTs) and cerebral amyloid angiopathy (CAA), Lewy bodies (LB) and vascular lesions but still not have dementia symptoms (Schneider *et al.* 2007, Kawas *et al.* 2015).

Population-based neuropathological studies offer the possibility of understanding the relationships between clinical syndromes, neuropathology, and genetics more widely. They have yielded important data in the population at large, for example, by establishing the associations between clinical dementia, ADRP, and the carriership of the *APOE e4* allele in elderly populations (Polvikoski *et al.* 1995, Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001, Pfeifer *et al.* 2002). Many of the population-based studies have also investigated mixed neuropathologies (Snowdon *et al.* 1997, Esiri *et al.* 1999, Fernando *et al.* 2004, Schneider *et al.* 2004, Petrovitch *et al.* 2005). Despite these advances, previous studies have yielded contradictory

results on the associations between CAA and dementia and there has been a lack of knowledge in some areas of neurodegenerative disorders, for example, on the prevalence of CAA subtypes (CAA Type 1 and CAA Type 2) and genetic risk factors of AD-type dementia in the population at large.

This study is a part of Vantaa 85+, a prospective and population-based neuropathological dementia study. The present study aimed to provide knowledge on the prevalence of different forms of neuropathologies, especially concerning CAA and other vascular pathologies, and to correlate the neuropathological data with clinical diagnoses of dementia and AD-associated gene loci in the very elderly.

2. REVIEW OF THE LITERATURE

2.1 Dementia

The definition of dementia includes cognitive decline, particularly the decline of episodic memory, and difficulties in learning new things, which are not features of normal ageing. As the dementing disease progresses, coping with everyday life becomes complicated. Other momentary or nutritional problems, such as infection, delirium or metabolic disorder or vitamin deficiency, are excluded (ICD-10, WHO 1992, American Psychiatric association, DSM-IV, 1994).

Dementia is an end stage of several mostly slowly progressive chronic neurodegenerative diseases leading to death, usually in 10-12 years (van Dijk et al. 1991, Molsa et al. 1995, Borjesson-Hanson et al. 2004). These diseases consist of neurodegenerative or vascular diseases, such as AD or VaD, or complications of brain damage, leading to neuronal loss and/or accumulation of specific proteins. Based on the clinical diagnosis, the most common neurodegenerative demented disease is AD (54%-76.5%), followed by VaD (17.9%-24%) (von Strauss et al. 1999) (Fratiglioni et al. 1991), LBD (5%) (Hogan et al. 2016), Frontotemporal lobar degeneration, FTL (5%) (Knopman et al. 2011). Less common causes, including Huntington's disease, Prion disease, and CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephopathy), together represent less than 5% of the demented individuals.

2.1.1. Clinical diagnosis of dementia

The clinical diagnosis of dementia is made via a combination of patient interview, neurological and neuropsychological examination, exclusion of a metabolic disease or deficiencies, imaging examination by computerized tomography (CT), positron emission tomography (PET) or magnetic resonance imaging (MRI), and possible cerebrospinal and genetic testing. However, an accurate specific dementia diagnosis without a neuropathological or genetical examination is not possible (Hyman et al. 2012).

Clinical diagnosis of dementia is defined by criteria such as ICD-10 (WHO 1992), Diagnostic and Statistical Manual of Mental Disorders, third revised edition (DSM III-R, American Psychiatric Association, 1987), DSM-III-R or DSM-IV (American Psychiatric Association, 1994). According to the clinical symptoms, dementia can be divided into mild, moderate or severe forms. The Mini-Mental State Examination (MMSE) test has been used in the estimation of cognitive impairment (Folstein et al. 1975).

There are standardized clinical diagnostic protocols for some of the dementia disorders, such as AD-type dementia (McKhann et al. 2011) or DLB (McKeith et al. 2005, McKeith et al. 2006), FTLD (Gorno-Tempini et al. 2011), and CADASIL (Rutten et al. 2014, Davous et al. 1998). On the other hand, for VaD, no standardized protocol exists.

2.1.2. Epidemiology of dementia

Dementia is not regarded as a part of normal ageing, although the incidence and prevalence in many dementia types increase with age (Jorm et al. 1987, Rocca et al. 1990, Jorm et al. 1998). Based on population-based clinical studies, the prevalence of dementia has been noted to be approximately 4% before the age of 75 years, 10-25% in subjects aged 75-85 years and 40% in those aged over 85 years and even 60% in subjects over 95 years (Table 1). The prevalence of dementia was estimated to be about 1.7% (92 232 / 5 402 627 individuals) in the Finnish population as a whole in 2012 (European Collaboration on Dementia EuroCoDe-Study 2013, ec.europa.eu/health) and 8.1% in the age group 65+. In 2014, the prevalence of mild dementia in Finland was estimated to be from 35 000 to 100 000, and moderate to severe dementia from about 85 000 to 93 000 (National Institute of Health and Welfare, Finland).

The incidence of dementia strongly increases with age (Table 1). In the 21st century, the incidence of dementia has been proposed to be 69-85 / 1000 person-years (Polvikoski et al. 2006). The incidence of dementia has been studied less than the prevalence. Furthermore, the incidence has mostly been studied in the younger age groups affected, that is, from middle age to elderly (aged 65-75), and less in old age, that is, in the elderly (aged 85 or more). The incidence of dementia for women is higher than for men. The lifetime risk for dementia for women was discovered to be 33% compared to 20% for men (Ott et al. 1995).

In Finland as well as in the other Western countries, life expectancy is expected to increase (Statistics Finland). The resulting change in the age structure is leading to an increasing number of elderly people and, consequently, to an increasing number of demented. The highest increase is expected among subjects aged 85+, leading to an increase in the prevalence of the demented. It has been estimated that in 2006, 7.6 million people, and in 2013, 10.9 million people suffered from dementia in Europe (European Collaboration on Dementia (EuroCoDe-Study) 2013, ec.europa.eu/health). In 2015, 46.8 million people suffered from dementia worldwide, estimated that this figure will more than double, by 2050 (Prince et al. 2015).

Table 1. Incidence (/1000 individuals/ year) and prevalence (%) of dementia in aged groups in Europe.

Age	Men (/1000 individuals/ year)	% of population	Women (/1000 individuals/ year)	% of population
60–64		0.2		0.9
65–69	2.4	1.8	2.5	1.4
70–74	6.4	3.2	4.7	3.8
75–79	13.7	7.0	17.5	7.6
80–84	27.6	14.5	34.1	16.4
85–89	38.8	20.9	53.8	28.5
90+	40.1	29.2	61.7	44.4
95+		32.4		48.8

Incidence according to Fratiglioni et al., 1999 and 2000 (Fratiglioni et al. 2000).

Worldwide prevalence and incidence of dementia, Drugs Aging 1999 (Lobo et al. 2000).

Prevalence in Europe (%) according EuroCoDe-Study (European Collaboraton on Dementia 2013, ec.europa.eu/health).

According to a more optimistic view, improved lifestyles, especially those avoiding the risk factors of atherosclerosis, have delayed the age of onset and thus diminished the incidence of dementia somewhat (Di Marco et al. 2014). The Neuropathology Group. Medical Research Council Cognitive Function and Aging Study (CFAS) study already showed that people born later than those born earlier in the 20th century, have lower risk for dementia (Matthews et al. 2013). Some population- or community-based studies have shown the diminishing of dementia prevalence rates, presumably due to the reduction of vascular risks and decline of strokes (Manton et al. 2005, Langa et al. 2008, Matthews et al. 2013). The most recent studies have shown that, despite the increased incidence of diabetes, hypertension and obesity, in contrast, the incidence of dementia has decreased between 2000 and 2012 (Langa et al. 2017).

2.2 Alzheimer's disease

2.2.1 Definition and clinical picture of Alzheimer's disease

Alzheimer's disease (AD) is the most common dementia syndrome. AD is a progressive neurodegenerative disorder with the clinical characteristics of progressive memory loss, lack of orientation, apraxia and, at the end of the disease, aphasia and cachexia. Before the characteristic AD symptoms, there can be a long, non-symptomatic preclinical period with no or mild cognitive impairment (MCI) that can last up to two decades (Hänninen et al. 2002, Lopez et al. 2003). In the

preclinical period, there are lesser degree ADRP findings (Troncoso et al. 1998, Petersen et al. 2001, Mitchell et al. 2002, Attems et al. 2006).

Typically, the first symptom in AD is the impairment of short-term memory. As the disorder progresses, the frequency and number of cognitive and behavioural symptoms increases. These include impairment of episodic memory, difficulties in learning and remembering new and recent things, language deterioration such as word-finding and visuospatial deficits, face and spatial recognition, and reading comprehension. In addition, impairment in problem solving and other executive functions are characteristic of AD (Cummings et al. 2004, McKhann et al. 2011).

In addition to typical AD symptoms there are some atypical AD clinical presentations frontal variant of Alzheimer's disease (fvAD), progressive aphasia or the posterior cortical atrophy (PCA) with possible visual failure (Benson et al. 1988) and mixed AD/ dementia. The clinicoradiological entity, the posterior cortical atrophy (PCA) form presented by D. Frank Benson in 1988, is characterized by early visual dysfunction (Renner 2004) and neurodegeneration in the posterior cortical regions of the brain (Benson et al. 1988). The consensus classification of the PCA types was made later, most recently in 2017 (Crutch et al. 2017).

2.2.2 Clinical diagnosis of Alzheimer's disease

Over the decades, there have been several sets of clinical criteria for AD. Currently, the main clinical neurological criteria for AD are the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and related Disorders Association (NINCDS-ADRDA), first published in 1984 and revised in 2011 (McKhann et al. 1984, McKhann et al. 2011).

Currently, the clinical lifetime diagnosis of AD also requires, in addition to neurological, radiological definition of AD-type changes such as atrophy in the inner temporal lobes, and lobar and hippocampal atrophy. These can be diagnosed by T2 or FLAIR MRI or CT techniques. The amyloid burden can be imaged by (PET) with fibrillar-amyloid-binding Pittsburgh Compound B, which, however, cannot differentiate between diffuse plaques and parenchymal or vascular A β (CAA) (Johnson et al. 2007). In addition to neurological and radiological examination, metabolic testing of A β , tau and phosphor-tau detected from cerebrospinal fluid can be used. Exclusion of other potential reasons behind the cognitive impairment is required.

2.2.3. Epidemiology of Alzheimer's disease

In clinical studies LOAD has been shown to be the most common dementing disorder, which has been thought to underlie 50-70% of dementias (Breteler et al. 1992). Both the prevalence and incidence of AD increase with age (Evans et al. 1989). In the population- or community-based studies on a 65+-year-old population in Europe, the prevalence of AD was estimated to be 4.4%-4.7% (Lobo et al. 2000, Prince et al. 2015). The incidence of AD in population-based studies on 65+-year-old Europeans has been estimated to be 19.4/1000 person-years (Fratiglioni et al. 2000). In the US, the incidence of AD has been estimated to be 15.0 (males 13.0; females 16.9) per 1000 person-years (Kawas et al. 2000, Kukull et al. 2002).

2.2.4. Risk factors for Alzheimer's disease

Age is the predominant risk factor for AD. In the clinical studies, the age-specific prevalence of AD almost doubles every five years after the age of 65. The incidence rate of AD increases almost exponentially with increasing age, until 85 years. The age range 80-89 years is the most affected (Fratiglioni et al. 2000, Lobo et al. 2000). Also, female gender seems to be a risk factor, as women are more often affected (Launer et al. 1999, Prince et al. 2015).

An AD-positive family history has shown to be a strong risk factor for AD; about one third of AD patients have a positive family history (Jayadev et al. 2008, Silverman et al. 2005). Having a first degree relative with AD more than doubles the risk for AD (Lautenschlager et al. 1996), emphasizing the role of genetic factors for both familial and sporadic AD (more in Section 4.3.). In addition to age and family history, vascular factors (hypertension, diabetes, hypercholesterolemia, smoking, obesity etc.) (Skoog et al. 1999, Kivipelto et al. 2001, Kivipelto et al. 2005) and psychosocial factors (low education, depression, stress) (Friedland 1993, Ownby et al. 2006, Sando et al. 2008) and head trauma (Mortimer et al. 1991, Luukinen et al. 2005) increase the risk for AD.

2.2.5. Neuropathology of Alzheimer's disease

The specific diagnosis of AD requires a neuropathological examination (McKhann et al. 2011, Hyman et al. 2012).

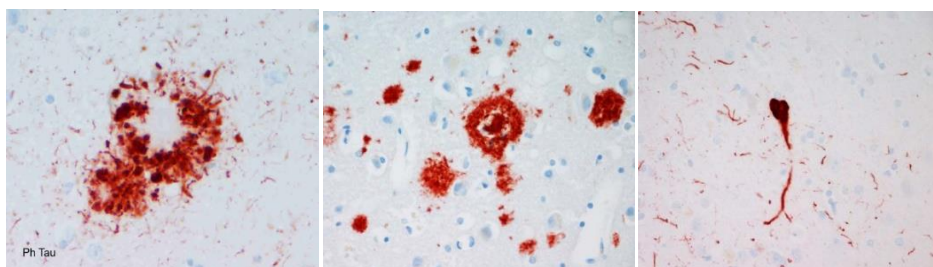
Macroscopically, AD is characterised by a reduced brain weight and volume due to neuronal loss (especially in cholinergic cells in the forebrains) and atrophy of the medial temporal lobes and limbic

regions of the hippocampus, resulting in ventricular enlargement, seen also in MRI studies (Laakso et al. 1995).

Microscopically, AD is characterised by marked neuronal and synaptic loss and accumulation of neuritic plaques (NP), and intraneuronal accumulation of hyper-phosphorylated tau protein as neurofibrillary tangle (NFT) formations (Braak et al. 1991, Mirra et al. 1991) (Figure 1.). The anatomical localisation of microscopical changes (NP and NFT) are notable (Table 3. and 2.).

In addition to the NP and NFT pathology in AD, A β is also observed in the parenchymal and meningeal cerebral vessel walls as CAA (Section 2.3). Reactive astrocytes, microglial cells (Itagaki et al. 1989) and glial activation, synapse loss and dystrophic neurites (DeKosky et al. 1990, Masliah et al. 1990, Masliah et al. 1993, Knowles et al. 1999) have been found particularly around NPs.

In addition to these accumulative findings, variable degenerative and spongiform changes, chronic inflammation with macrophages, microglia cells (Di Patre et al. 1999) and circulatory immune system cells (Heneka et al. 2015, Zenaro et al. 2015) are seen. Furthermore, TAR DNA-binding protein-43 (TDP-43) inclusions, distinct from neurofibrillary tangles, are detected in 23% to 57% of AD cases (Amador-Ortiz et al. 2007, Arai et al. 2009, Josephs et al. 2014), and white matter rarefaction has been observed in half of the AD cases (Englund et al. 1998).



a. Senile plaque

b. Neuritic plaque

c. Neurofibrillary tangles

Figure 1. (A). Senile plaque. Non-fibrillar A β aggregation, no recognizable neuritic pathology. (B). Neuritic plaque (NP) with a specific amyloid core and possible accumulation of hyperphosphorylated tau protein (C). Intraneuronal accumulation of the tau protein consists of aggregates of misfolded hyperphosphorylated tau protein forming neurofibrillary tangles (NFT) (Grundke-Iqbal et al. 1986). In addition to the tangles, hyperphosphorylated tau also accumulates as intraneuronal neuropil threads (NT) (Hyman et al. 2012). Magnification 400x. Courtesy of Adjunct Professor Maarit Tanskanen.

2.2.5.1 Neuropathological criteria for Alzheimer's disease

At the beginning of 1990, the ADRP pathology was assessed by applying silver (such as modified Bielshowsky) stained sections, and thus the NP and NFT lesion were identified and noted. Plaques have been divided morphologically into diffuse, cored and neuritic plaques. Diffuse plaques are frequently found in the brain parenchyma in normal ageing (Davies et al. 1988). NPs are defined as plaques with a specific amyloid core surrounded by dystrophic neurites (Mirra 1991) and possible accumulation of hyperphosphorylated tau protein, associated with neurodegeneration, neuronal injury and AD (Mirra et al. 1991) (Section 2.2.5.2.). NFTs are defined as intraneuronal accumulation of aggregates of misfolded hyperphosphorylated (HP) tau protein (Grundke-Iqbal et al. 1986) (Section 2.2.5.3.).

In 1907, Alzheimer described senile plaques and NFTs in demented individuals. Almost eighty years later, in 1985, Khachaturian published widely applied neuropathological diagnostic criteria for AD, based on the number of NP and NFT in the brain cortex in relation to age and clinical situation.

Braak devided, in 1991, silver-positive NFT pathology in proceeding six stages 0-VI (Braak et al. 1991) (Table 2.).

Table 2. Braak stages 0-VI.

Stage	Brain region containing NTF pathology
0	no NFT pathology
I	Transentorhinal region
II	Entorhinal region
III	The neocortex of the fusiform and lingual gyri, Hippocampal CA1
IV	The disease process progresses more widely into neocortical association areas, Insular cortex
V	Superior temporal gyrus, Peristriate region
VI	Parastriate area, Striate area

In Braak staging method of six stages (0-VI), NFT pathology was originally assessed of 100µm thick sections stained with the Gallyas silver method (Braak et al. 1991).

In 1991, the neuropathological diagnosis criteria were recorded in the Consortium to Establish a Registry of Alzheimer Disease (CERAD) by Mirra *et al.* (Mirra *et al.* 1991). These criteria were scored from 0 to 3 and based on a semi-quantitative analysis, applying silver or thioflavin S stained sections of cortical NPs combined with Information on the patient age and the clinical history of dementia (Table 3.). Diffuse plaques were not included (Mirra *et al.* 1991). The CERAD criteria led to definite, probable or possible AD diagnoses.

In 1997, the NIA-RI criteria (The National Institute on Aging and Reagan Institute working group on diagnostic criteria for the neuropathological assessment of Alzheimer's disease, 1997) were published. These criteria aimed to determine the likelihood (low, moderate or high) of dementia of the autopsied individual being caused by ADRP changes. The NIA-RI criteria combine the CERAD score with the immunohistochemical stained NFT and neutrophil thread (NT) depositions (NIA-RI consensus 1997).

In the NIA-RI criteria, Braak stages were combined into 4 categories: (0) no NFT pathology, (I-II) NFT predominantly in the entorhinal or closely related cortex, (III-IV) NFT more abundant in the hippocampus and amygdala, (V-VI) NFT throughout the neocortex. If the CERAD score was frequent and the Braak stage was either 5 or 6, the likelihood that dementia was caused by the AD-type pathology was high, and the neuropathological diagnosis of AD could be set. It is noteworthy that clinical dementia of the patient was a prerequisite for the neuropathological diagnosis of AD according to the NIA-RI criteria (NIA-RI consensus 1997).

Currently the protein-based immunohistochemical (IHC) techniques are frequently applied with antibodies against A β protein and phospho-tau in the routine diagnostics (Braak *et al.* 2011). Silver staining and IHC methods have been shown to be comparable. However, staining with HP-tau IHC is more pronounced compared to silver stains, and highlights predominantly NTs rather than NFT (Alafuzoff *et al.* 2008).

The diagnostic neuropathological criteria of AD were updated some years ago (Hyman *et al.* 2012, Montine *et al.* 2012) (Table 3.) The new criteria differ from the NIA-RI criteria in that they do not require a clinical history of dementia or dementia diagnosis. According to these new criteria, the neuropathological AD diagnosis is given based on the combination of the A β plaque score (Thal *et al.* 2002b), Braak stage and CERAD score as the "ABC score", regardless of any clinical history of dementia. Possible CAA (Vonsattel *et al.* 1991) or, if examined, the occurrence of the $\epsilon 4$ allele of APOE (Thal *et al.* 2008b) should be reported.

Table 3. The classification of ADRP according to the National Institute on Aging - Alzheimer's Association.

Aβ plaque score^A	NFT stage^B	Neuritic plaque score^C
A0 no A β or amyloid plaques	B0 no NFTs	C0 no neuritic plaques
A1 Thal phases 1 or 2	B1 Braak stage I or II	C1 CERAD score sparse
A2 Thal phase 3	B2 Braak stage III or IV	C2 CERAD score moderate
A3 Thal phases 4 or 5	B3 Braak stage V or VI	C3 CERAD score frequent

Table modified from Hyman *et al.* (Hyman et al 2012).

A: modified from Thal *et al.* (Thal et al. 2002b). B: modified from Braak (Braak et al. 1991) for silver-based histochemistry or phospho-tau immunohistochemistry. C: modified from CERAD (Mirra et al. 1991)

Thal phase 1: neocortical deposits; frontal, parietal, temporal and occipital cortex

Thal phase 2: Allocortical deposits, hippocampal formation, insular, cingulate and entorhinal cortex, amygdala

Thal phase 3: Deposition in diencephalon nuclei and striatum, hypothalamus, thalamus, basal ganglia, basal forebrain nuclei

Thal phase 4: Deposition in brainstem nuclei (substantia nigra, red nucleus, central grey, superior and inferior collicle, inferior olivary nucleus, intermediate reticular zone), midbrain, medulla oblongata

Thal phase 5: Deposition in cerebellum and additional brainstem nuclei (pontine nuclei, locus coeruleus, parabrachial nuclei, reticulo-tegmental nucleus, dorsal tegmental nucleus, and oral and central raphe nuclei, pons, cerebellum)

2.2.5.2. Molecular basis of the amyloid β aggregates

Amyloid has been noted to be the major protein component of brain plaques (Masters et al. 1985). Plaques have been shown to be composed mainly of $A\beta$ (Kang et al. 1987). $A\beta$ is produced from the Amyloid precursor protein (APP) by proteolytic cleavage in the brain, mainly in neuronal cells but also in smooth muscle cells, pericytes and endothelial cells (Kang et al. 1987, Kalaria et al. 1996, Burgermeister et al. 2000). APP is an acute phase transmembrane glycoprotein, expressed in various cell types all over the body and its production increases with tissue or axon injury. APP also affects cell division, synaptogenesis and axonal transport (Zheng et al. 2006).

APP is cleaved by α , β and γ secretases. $A\beta$ is produced by enzymatic cleavage of β and γ secretases (Kang et al. 1987, Reinhard et al. 2005). There are at least two proteins functioning as β secretases; beta-amyloid cleavage enzyme (BACE) 1 and 2, situated mostly in endosomes. The β -pleated sheet conformation results in more insoluble structures. $A\beta$ peptides contain a fairly insoluble β -pleated sheet conformation and have been shown to have the tendency to self-assemble aggregates (Glennner et al. 1984, Lambert et al. 1998) and form mature amyloid aggregates (Dickson et al. 1997).

Amino or carboxy-terminal and posttranslational modifications by γ secretase cause variation in the length of the $A\beta$ fibril. In the human brain, $A\beta$ has been noted to be of 36-43 amino acids (aa) in length, most often 40 or 42 aa (Haass et al. 1992). The $A\beta_{1-40}$ and $A\beta_{1-42}$ fibrils are the most typical forms in the brain parenchymal and vascular aggregates. In the normal physiological condition, in the alpha (α) secretase pathway, APP is cleaved in the middle of the $A\beta$ peptide, inhibiting the $A\beta$ formation and producing an α helix (Sisodia et al. 2002) (Figure 2).

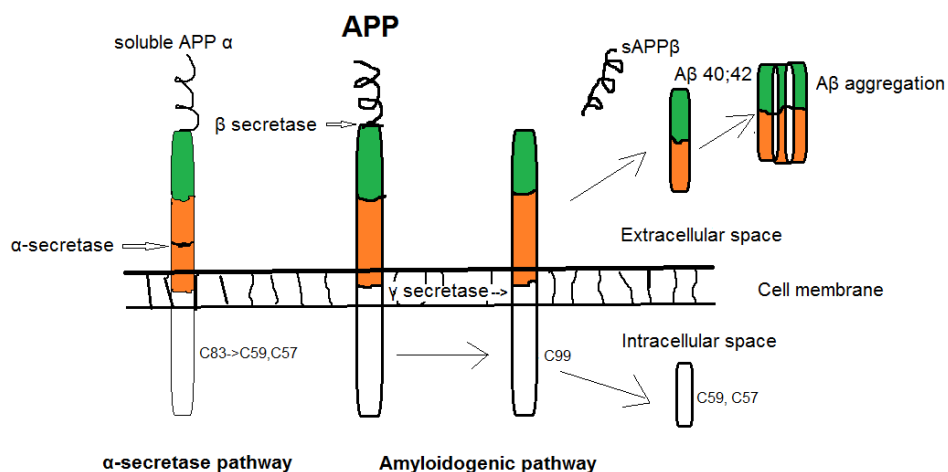


Figure 2. Proteolytic cleavage of APP by β secretase in the amino terminus and γ secretase in the carboxyl terminus generates an A β peptide with a length of usually A β -40 or A β -42 in the human brain, A β -40 being the main product. A β is produced by the proteolytic process from the transmembrane amyloid precursor protein (A β PP) by enzymatic cleavage by β and γ secretases. In the normal physiological condition, APP is mainly cleaved by the α -secretase to form an α -helix (Modified from several publications e.g. Zhang et al. 2010).

Single monomers of A β have been considered harmless, but the self-association of those monomers has been noted to make the peptides neurotoxic (Lambert et al. 1998). A β -42 has been shown to form aggregates more easily than A β -40. The extracellular accumulation of A β as plaques (diffuse, cored and neuritic) is mainly the result of aggregated A β -42 (Iwatsubo et al. 1995), whereas the shorter and more soluble A β 1-40 tends to predominate in CAA (Castano et al. 1996, Harper et al. 1997). The A β ₄₀ form is able to diffuse over larger distances along the perivascular drainage pathways, which would explain its abundance in vascular amyloid deposits (Van Dorpe et al. 2000). In contrast to the aggregated forms, soluble A β oligomers are considered highly neurotoxic components (Lambert et al. 1998) .

2.2.5.3. Tau-related pathology

Accumulation of the intraneuronal hyperphosphorylated tau protein is one of the main diagnostic features of AD.

In normal conditions, the tau protein stabilizes microtubules and promotes microtubule assembly. Six different tau isoforms are expressed as the result of alternative splicing of exons. Some degree of tau accumulation has been noted with normal ageing (Braak et al. 2011), but the severe neocortical NFT pathology almost always associates with cognitive impairment or dementia (Baner et al. 1993, Riley et al. 2002). The A β oligomers are believed to promote the phosphorylation of tau (De Felice et al. 2008). Accumulation of the tau protein into NFTs can either be a secondary response (for example caused by the A β oligomers) to injury (Goedert et al. 2004) or be caused by a tau gene mutation. Therefore, the tau pathology is not specific for AD (Goedert et al. 2004), and NFTs can also be detected in other degenerative diseases, such as Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease or traumatic conditions (Goedert et al. 2004).

2.2.5.3.1 Primary age-related tauopathy

The term "primary age-related tauopathy" (PART) was invented to describe the presence of NFTs in the absence of A β plaques, a common finding in the brains of aged individuals (Crary et al. 2014). The cognitive status in PART varies from normal to cognitive changes, mostly mild. PART has been proposed to be classified as a part of AD (Duyckaerts et al. 2015), probably being the precursor of AD with both tau and amyloid pathology (Duyckaerts et al. 2015). This entity is still under debate.

2.2.5.4. Atypical Alzheimer's disease-related pathology

In addition to typical AD with Braak-type spearing of NFT pathology, there are some AD cases with atypical NFT spearing. In the atypical form of AD, NFTs have been noted to spear at either the hippocampal (HpSp) or limbic-predominant (LP) neurofibrillary forms (Murray et al. 2011). HpSp and LP have been thought to account for as much as 25% of AD cases. HpSp has been discovered to have a higher NFT density in the cortical areas and a lower one in the hippocampus, whilst LP has the opposite. Both HpSp and LP show less atrophy in the hippocampus (Murray et al. 2011). The *MAPT H1H1* genotype has been noted to be common in LP, but no clear difference has been reported in the *APOE ϵ 4* allele status among the AD subtypes (Murray et al. 2011). Neurofibrillary tangle-predominant dementia (NFTD) has been shown to differ from the HpSp and LP subtypes of AD especially with its paucity of amyloid β pathology (Janocko et al. 2012). NFTD shows NFT mainly in limbic structures (Jellinger et al. 2007b, Duyckaerts et al. 2009) with no, or very few, NPs. Instead, there are severe NFTs in the allocortical areas (entorhinal region, subiculum, Cornu Ammonis1 (CA1), amygdala) (Nelson et al. 2009). The cases are older and the prevalence of the *APOE ϵ 4* allele is lower than in general AD (Jellinger et al. 2007b). The clinical progression has also been noted as being slower than in typical AD (Jellinger et al. 2007b).

In the plaques-only type, there are very few neocortical tangles (Terry et al. 1987), but both the brainstem and cortical Lewy body pathology may be found (Hansen et al. 1993).

2.2.6. Inflammation associated with Alzheimer's disease-related pathology

In AD, the abnormal A β deposition, and also NFT to some extent, promote an immunological reaction in the central nervous system. The immunological reaction and inflammation are proposed to influence the entire clinical picture of AD (Di Patre et al. 1999) and be an important part of its pathological process. In that process, microglia cells and perivascular macrophages are the main immune system cell populations. Inflammation has been noted to associate with many types of A β ; plaques, soluble A β or CAA.

(a.) Activated microglia have been observed near the A β plaques. A β can activate microglia, for example by binding to the RAGE receptor (Yan et al. 1998). Activated microglia can release pro-inflammatory components as cytokines, complement components, free radicals and nitric oxide (Griffin et al. 1998). This inflammatory reaction has been documented as associating specifically with the neuritic A β plaques (Rogers et al. 2002) and is believed to be induced by A β (Rogers et al. 1992). This chronic-type inflammatory reaction is also combined with circulating immune system cells (Heneka et al. 2015, Zenaro et al. 2015). Inflammation is considered to contribute to neuronal dysfunction and death. Activated microglia can phagocytose A β in its diffuse state but possibly not when it is forming neuritic plaques (Sheng et al. 1997).

(b.) Soluble A β oligomers have also been thought to trigger the cascade of inflammation and activation of the complement leading to an impaired permeability of the blood-brain barrier (BBB) and cell toxicity, resulting in synaptic loss and neuronal injury (Walsh et al. 2007).

2.2.7. Hypothesis on the pathogenesis of Alzheimer's disease

The most famous theory on the origin of AD is the amyloid cascade hypothesis. It was described after the discovery of familial mutations in the *APP* or *PS* genes leading to an overproduction of A β (Hardy et al. 2006, Selkoe 2006, Hardy et al. 1991, Glenner et al. 1984, Selkoe et al. 1991, Hardy et al. 1992). According to the amyloid cascade hypothesis, A β accumulation in the brain parenchyma leads to NFT formation, and neuronal loss and dysfunction (Selkoe et al. 2016).

However, the theory has been criticized, as there is no confirmed evidence for the overproduction of A β in sporadic AD (Weller et al. 2008), despite some sporadic AD cases with *APP* mutations (Biffi et al. 2011). Other theories are related to the metabolism of A β and failure in the elimination of A β

from the brain by 1. enzymatic degradation, 2. absorption into the blood, or 3. the lymphatic drainage pathway (Weller et al. 2008).

Failure in A β elimination is suggested to lead to an imbalance between the production and clearance of A β , and has been thought to be an initiating factor in sporadic LOAD, as opposed to the increased formation of A β (Guenette et al. 2003, Mawuenyega et al. 2010), as seen in FAD.

Increased A β proportion in the brain has been thought to lead to extracellular A β accumulation in NPs (Hardy et al. 1991) or aggregations in vessel walls as CAA (see below 2.3). Comorbid pathology, such as atherosclerotic brain ischemia, can also increase A β production through the activation of *BACE1* (Sun et al. 2006).

2.2.8. Genetic background of Alzheimer's disease

Based on the genetic and clinical findings, AD can be divided into two main forms. Rare (1-5% of AD) familial AD (FAD) form starts at an earlier age (often < 65 years) and is caused by autosomal dominant mutations in the *Amyloid Precursor Protein (APP)* (Goate et al. 1991) and *Presenilin 1 (PS1)* or *2 (PS2)* (Levy-Lahad et al. 1995, Rogaev et al. 1995, Scheuner et al. 1996) genes. Mutations in *APP*, *PS1* and *PS2* contribute between 35 to 60% of FAD (Gatz et al. 2006) and these genes are related to A β production. Some of these *PS1* mutations are associated with eosinophilic cotton wool plaques lacking the dense core seen mainly in FAD (Crook et al. 1998, Tabira et al. 2002).

The more common form, LOAD, has been suggested as being linked to reduced clearance of A β , rather than to an increased production of A β as in the familial forms. In addition, the symptoms in the LOAD usually begin later, after 60-75 years of age. Compared to FAD, LOAD has been thought to have a moderate inherited component, which is mediated mainly through *APOE ϵ 4* (Gatz et al. 2006, Bertram et al. 2010). The AD risk is more than twice as high in first degree relatives of AD patients (Lautenschlager et al. 1996). The hereditary component of AD has been estimated to be 60-80% in twin studies (Bergem et al. 1997, Pedersen et al. 2001). In some epidemiological studies, the genetic component of AD has been estimated as varying from 25-40% (Van Broeckhoven et al. 1995, Rosenberg et al. 2000) to 58-79% (Gatz et al. 2006). Various methods of genetic mapping have been used in order to discover the variations that affect the AD risk in the genome.

2.2.8.1. Linkage analysis and candidate gene analysis

One of the first genetic mapping methods to study the genetics of AD was linkage analysis. In linkage analysis, the segregation of closely located, recombined areas of chromosomes with the phenotype of interest is observed. Linkage analysis has been used most successfully in studies of large families and Mendelian traits.

Linkage analysis has played an important role in the genetic research on AD. For example, first, a linkage peak on chromosome 21 was detected in AD families (St George-Hyslop et al. 1987). This peak was later shown to represent the *APP* gene by using candidate gene analysis (Kang et al. 1987, Robakis et al. 1987, La Fauci et al. 1989).

Candidate gene analysis is based on hypotheses generated by previous research. Prior research identifies a candidate gene or genetic area, the association of which to the specific phenotype is then tested.

The AD-associated *APOE* $\epsilon 4$ allele was first identified by a candidate gene study (Corder et al. 1993, Strittmatter et al. 1993) after genetic linkage studies had reported a suspect locus on chromosome 19 (Pericak-Vance et al. 1991). *APOE* has three common isoforms: $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, encoded by two polymorphic sites (Zannis, Breslow 1982). In later studies, the homozygosity of *APO* $\epsilon 4$ has been noted to increase the risk of AD tenfold (Farrer et al. 1997).

2.2.8.2. Genome-wide association studies

Genome-wide association studies (GWAS) facilitate the observation of variation at the whole genome level, free of previous hypotheses. The data of the International HapMap project with 500 000 genotyped SNPs enabled the development of the GWAS studies in 2005 (International HapMap Consortium 2005).

In GWAS, the comparisons are made between the phenotype (case and control) and the allele frequencies of the genotype (most commonly SNPs). No prior hypotheses are needed. Challenges of the GWAS approach include its dependence on the capability of the analysis programs, increased risks of false negative or false positive results, and failure to identify rare variants. Those pitfalls can be avoided, for example by large cohorts, meta-analyses of several studies and strict criteria for statistical significance (p -value $< 5 \times 10^{-8}$) (Hindorff et al. 2009, Korte et al. 2013).

GWAS studies have confirmed the previously discovered strong association of *APOE* $\epsilon 4$ with AD (Bertram et al. 2007, Reiman et al. 2007a, Carrasquillo et al. 2009, Harold et al. 2009, Lambert et al. 2009, Seshadri et al. 2010, Hollingworth et al. 2011, Lambert et al. 2013) and later with neuropathologically defined AD (Shulman et al. 2013, Beecham et al. 2014). *APOE* $\epsilon 4$ has been

noted to associate significantly with all the AD-type neuropathologies: CERAD score, Braak stage and CAA in the GWAS-based study by Beecham (Beecham et al. 2014).

2.2.8.3. GWAS-based Alzheimer's disease risk loci

In addition to *APOE ε4*, GWAS studies have identified around thirty other AD-associated genetic loci. The studies are mostly based on large cohorts of clinical-based AD samples (Bertram et al. 2007, Harold et al. 2009, Lambert et al. 2009, Corneveaux et al. 2010, Hollingworth et al. 2011, Wijsman et al. 2011, Lambert et al. 2013, Shulman et al. 2013, Beecham et al. 2014) .

Table 4. Identified AD risk loci based on meta-analysis or genome-wide association studies.

LOCI	Polymorphisms linked to AD	Publication
ABCA7	rs3752246	(Naj et al. 2011)
ABCA7	rs4147929	(Lambert et al. 2013)
ABCA7	rs3764650	(Hollingworth et al. 2011) (Shulman et al. 2013)
ABCG1	21-43678066	(Beecham et al. 2014)
APPnear	rs2829887	(Shulman et al. 2013)
BIN1	rs6733839	(Lambert et al. 2013)
BIN1	rs7561528	(Harrold et al. 2009)
BIN1	rs744373	(Harrold et al. 2009) (Hollingworth et al. 2011) (Seshardi et al. 2010)
BIN1	rs12989701	(HU et al. 2011)
CASS4	rs7274581	(Lambert et al. 2013)
CD2AP	rs10948363	(Hollingworth et al. 2011)

		(Lambert et al. 2013)
CD2AP	rs9349407	(Naj et al. 2011) (Shulman et al. 2013)
CD33	rs3865444	(Naj et al. 2011) (Hollingworth et al. 2011)
CD33	rs51727962	(Lambert et al. 2013)
CELF1	rs10838725	(Lambert et al. 2013)
CLU	rs11136000	(Seshardi et al. 2010) (Harold et al. 2009)
CLU	rs1532278	(Naj et al. 2011)
CLU	rs9331896	(Lambert et al. 2013)
CR1	rs1408077	(Harold et al. 2009)
CR1	rs3818361	(Harold et al. 2009) (Hollingworth et al. 2011)
CR1	rs6656401	(Lambert et al. 2013)
CR1	rs6701713	(Harold et al. 2009) (Shulman et al. 2013)
EPHA1	rs11771145	(Seshardi et al. 2010)
EPHA1	rs11767557	(Naj et al. 2011)
EXOC3L2near	rs597668	(Seshardi et al. 2010)
FERMT2	rs17125944	(Lambert et al. 2013) (Ruiz et al. 2014)

GAB2	rs2373115	(Reiman et al. 2007)
GALNT7	rs62341097	(Beecham et al. 2014)
HLA-DRB5/1	rs9271192	(Lambert et al. 2013)
INPP5	rs35349469	(Lambert et al. 2013) (Ruiz et al. 2014)
MEF2C	rs190982	(Lambert et al. 2013) (Ruiz et al. 2014)
MS4A6A	rs983392	(Lambert et al. 2013)
MS4Acluster	rs610932	(Hollingsworth et al. 2011) (Harold et al. 2009)
MS4Acluster	rs670139	(Hollingsworth et al. 2011)
MS4Acluster	rs4938933	(Naj et al. 2011)
NME8	rs2718058	(Lambert et al. 2013)
PICALM	rs3851179	(Harold et al. 2009) (Seshardi et al. 2010)
PICALM	rs10792832	(Lambert et al. 2013)
PICALM	rs561655	(Naj et al. 2011)
PTK2B	rs28834970	(Lambert et al. 2013)
Region chr9	9-129356304	(Beecham et al. 2014)
SLC24A4	rs10498633	(Lambert et al. 2013)
SORL1	rs11218343	(Lambert et al. 2013)
TREM2	rs75932628	(Jonsson et al. 2013)

		(Guerreiro et al. 2013)
TRIP4	rs74615166	(Ruiz et al. 2014)
ZCWPW1	rs1476679	(Lambert et al. 2013) (Ruiz et al. 2014)

In addition to studies based on the clinical diagnosis of AD, a few GWAS studies have recently been published with neuropathologically examined samples (Shulman et al. 2013, Beecham et al. 2014). In these neuropathologically examined GWAS studies, about half of the previously identified AD risk loci have been noted to be associated with either NP or tangle pathology, or both (Table 5). No association with CAA has been determined (Beecham et al. 2014).

Table 5. AD risk loci (other than *APOE ε4*) based on GWAS studies with clinically defined AD and associations with ADRP (neuritic plaques and neurofibrillary tangle pathology)

GENE	chr	Pathway/function, if known	NP +/-	NFT +/-
ABCA7	19	immune system, lipid metabolism, Aβ metabolism	+ (Shulman et al. 2013) + (Beecham et al. 2014)	+ (Beecham et al. 2014)
ABCG1	21	immune system, lipid metabolism		
APP	21	Aβ cleaving, lipid metabolism	Near APP, (Shulman et al. 2013)	
APOE	19	lipid metabolism		
BIN1	2	endocytosis, synaptic function, modulation of tau pathology	+ (Beecham et al. 2014) - (Shulman et al. 2013)	+ (Beecham et al. 2014))
CASS4	20	regulation of cell spreading and adhesion	+ (Beecham et al. 2014)	+ (Beecham et al. 2014))
CD2AP	6	endocytosis, synaptic function	+ (Shulman et al. 2013)	
CD33	19	immune system, synaptic function	+ (Beecham et al. 2014) - (Shulman et al. 2013)	
CELF1	11			
CLU	8	immune system, lipid metabolism, Aβ metabolism	- (Shulman et al. 2013)	+ (Beecham et al. 2014)
CR1	1	immune system, Aβ metabolism	+ (Shulman et al. 2013)	
EXOCC3L2	19			
EPHA1	7	immune system, synaptic function	- (Shulman et al. 2013)	
FERMT2	14	modulation of angiogenesis		

GAB2	11	might protect cells against tangle formation		
GALNT7	4			
HLADRB1	6	immune system		
HLADRB5	6	immune system		
INPP5D	2	immune system, APP metabolism		
MEF2C	5	immune system, synaptic function	+ (Beecham et al. 2014)	+ (Beecham et al. 2014)
MS4A	11	immune system, hippocampal synaptic function	+ (Beecham et al. 2014) - (Shulman et al., 2013)	
NME8	7	neuronal cell proliferation and differentiation		
PICALM	11	endocytosis, synaptic function	+ (Beecham et al. 2014) - (Shulman et al. 2013)	+ (Beecham et al. 2014)
PTK2B	8	hippocampal synaptic function		
Region chr9	9			
SLC24A4	14	neural development,		
SORL1	11	endocytosis, lipid transportation and APP metabolism		+(Beecham et al. 2014)
TREM2	6	immune system		
TRIP4	15	nucleus signalling, immune system		
ZCWPW1	7	epigenetic regulation		+(Beecham et al. 2014)

In general, the AD risk loci encode proteins influencing different pathways involved in cholesterol metabolism, the immune system, inflammation and immune response, synaptic and membrane function, and also participating in A β metabolism and Tau interactions (Rogaeva et al. 2007, Kim et al. 2008, Castellano et al. 2011, Kim et al. 2013, Ulrich et al. 2014).

Loci such as Clusterin (*CLU*) and ATP-Binding Casette, sub-family A, member 7 (*ABCA7*) have been stated to have a role in both cholesterol metabolism and the immune system. They both have been demonstrated to be associated with NFT pathology (Beecham et al. 2014), and *ABCA7* has been noted to be associated with NP pathology both in Schulman's and Beecham's publications (Shulman et al. 2013, Beecham et al. 2014).

CLU and *ABCA7* seem to influence A β metabolism, as do APP, Inositol polyphosphate-5-phosphatase (*INPP5*) and Sortilin-Related receptor 1 (*SORL1*) (Morgan 2011, Lambert et al. 2013). *CLU* and Complement component (3b/4b) receptor 1 (*CR1*) have been noted to bind A β peptides and clear them from the brain (Lambert et al. 2009). Shulman et al. noted the association between *CR1* and NPs (Shulman et al. 2013) but Beecham did not (Beecham et al. 2014).

APP takes part in the A β metabolism (Morgan 2011, Lambert et al. 2013) and, in addition to influencing FAD, an SNP at the *APP* locus (rs2829887) seems to associate with NP pathology in sporadic AD cases (Shulman et al. 2013). The Phosphatidylinositol Binding Clathrin Assembly protein (*PICALM*), Binding integrator 1 (*BIN1*), Phosphatidylinositol Binding Clathrin Assembly protein (*CD2AP*) and *SORL1* genes have been shown to modulate A β production via the endocytosis of APP (Guerreiro et al. 2010) and *ABCA7*, *CLU*, *SORL1* by regulating APP processing (Guerreiro et al. 2010). *BIN1* has been noted to modulate the tau pathology (Chapuis et al. 2013). Many of the loci involved in A β metabolism, *ABCA7*, *BIN1*, *PICALM* and *SORL1*, have been shown to associate with the neuropathologically defined AD-type dementia (Beecham et al. 2014). In addition, *CASS4*, *CD33* molecules (*CD33*), *MEF2C*, *MS4A6A* and *ZCWPW1* are associated with the neuropathologically defined AD-type dementia (Beecham et al. 2014), but they influence pathways other than those involved in A β metabolism.

CD33 and the *MSA4 cluster* have a role in the immune system, as have the *CLU*, *CR1*, *ABCA7*, *TREM2* and *EPHA1* loci. *CD33* and *TREM2* have been shown to involve the local uptake of A β peptides by microglia. A great many of the *CLU*, *CR1*, *ABCA7* *MSA4* and *CD33* loci have been noted to associate with one or other of the neuropathological variables, NP or NFT pathology (Shulman et al. 2013, Beecham et al. 2014).

2.3. Cerebral amyloid angiopathy

2.3.1. Definition of cerebral amyloid angiopathy

CAA means the deposition of A β in the cerebral cortical or and leptomeningeal blood vessels. This deposition takes place mainly in the arteries, but capillaries and veins can also be affected (Vinters et al. 1987, Revesz et al. 2003). The most common type of CAA is the sporadic, which is associated with AD. 'Amyloid' means a protein that 1) binds to the Congo red dye, 2) folds into spatial beta-pleated sheet structures, and 3) forms insoluble fibrils, mainly in the extracellular space. In sporadic CAA, the amyloid protein is A β (Glenner et al. 1984, Prelli et al. 1988, Haass et al. 1992). There are some rare, and mostly hereditary, forms of CAA, in which the amyloid protein is other than A β . In addition to protein fibrils, amyloid fibrils contain other molecules, such as glycosaminoglycans and p-component. In CAA, the vessel walls can be thicker, hyaline-like and, at an advanced stage, contain fibrinoid necrosis, a double-barrelled lumen and microaneurysms (Revesz et al. 2002).

Using Congo red, amyloid is visualized by showing the typical red to green bi-refringence in the polarized light (Sipe et al. 2000). CAA can also be visualized by immunofluorescence for the β sheet-

specific Thiophlavin T and S dyes. The fibril protein in the amyloid fibres can be determined using immunohistochemistry against the A β peptide (Figure 3).

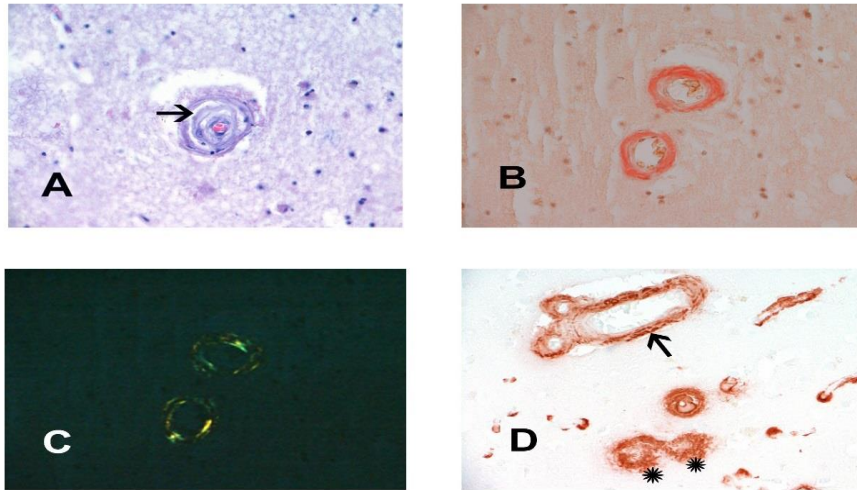


Figure 3. (A) Cerebral amyloid angiopathy. A thickened and split (arrow) vessel wall caused by CAA (hematoxylin-eosin stain). (B) Amyloid appears orange-red when visualized with Congo-red staining and (C) green in polarized light. (D) Immunohistochemical staining of A β in a vessel wall (arrow) and in senile plaques*(x400). Photo: Adjunct Professor Maarit Tanskanen.

2.3.2. Metabolism of amyloid β : production and elimination

A β peptides have been detected in the brain and cerebrospinal fluid of individuals of all ages (Haass et al. 1992, Seubert et al. 1992, Walsh et al. 2000), and the soluble A β concentration has been noted to correlate with neuronal activity (Shoji et al. 1992, Naslund et al. 1994). In the brain, A β can be carried long distances in the extracellular space, mainly by passive diffusion and by binding to transport proteins such as APOE and the α 2 macroglobulin. In addition, astrocytes and microglial cells can absorb A β and migrate with it into other brain regions, as has been shown mainly in mouse models (Jensen et al. 1994, Wyss-Coray et al. 2003, Mandrekar et al. 2009). In mouse models, the soluble A β oligomers have been thought to be able to change between extracellular and intracellular locations (Gaspar et al. 2010).

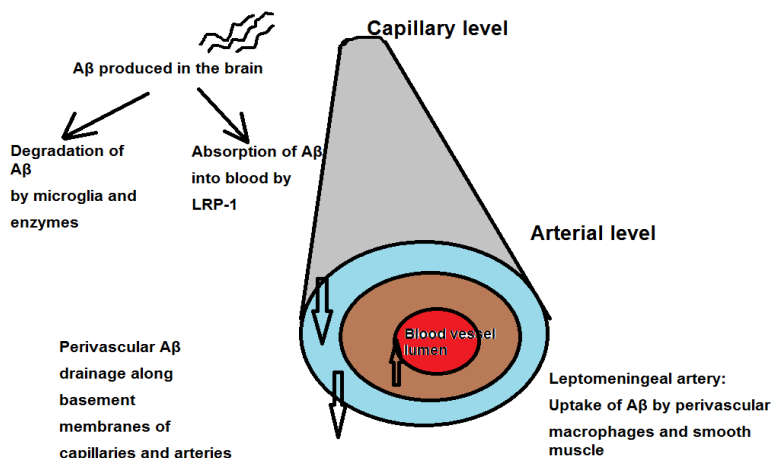


Figure 4. Aβ is produced in the brain by the parenchymal and vascular wall cells. The elimination of Aβ occurs through its absorption into blood via the arterial wall smooth muscle cells by low density lipoprotein receptor-related protein 1 (LRP-1) and P-glycoprotein. In the brain parenchyma, vascular smooth muscle cells or perivascular macrophages degrade Aβ via enzymes such as neprilysin and the insulin-degrading enzyme. Part of the Aβ is eliminated by perivascular lymphatic drainage along the basement membranes of capillaries and arteries, probably to cervical lymph nodes.

In the normal brain, soluble Aβ is thought to be eliminated by three separate routes: (1.) enzymatic degradation, (2.) absorption to blood, and (3.) along the lymphatic drainage pathway.

(1.) In the normal brain parenchyma, soluble Aβ is eliminated and degraded by such cells as microglia, astrocytes, oligodendroglia, neurons and perivascular macrophages by degradation and an enzymatic reaction. The neprilysin protease (Farris et al. 2007) and insulin-degrading enzyme (IDE) (Leissring et al. 2003) are the most important enzymes. IDE mainly degrades the soluble monomeric Aβ, whereas neprilysin can also tackle the aggregated Aβ. In addition, enzymes such as plasmin, endothelin and angiotensin-converting enzymes, matrix metalloproteinases and cathepsin B and D also participate in the enzymatic degradation of Aβ (Miners et al. 2008).

(2.) In the normal brain, absorption of soluble Aβ through the BBB is receptor-mediated (Zlokovic 2002). There are mainly two receptors for this in the endothelium: glycosylated end products (RAGE) and the low density lipoprotein receptor (LPR) (Zlokovic et al. 2005, Deane et al. 2004). Low density lipoprotein receptor-related protein 1 (LRP-1) is an endothelial transmembrane protein involving Aβ absorption and transport into the blood. The shorter Aβ-40 peptide is absorbed more rapidly than the longer Aβ-42 via LRP-1 (Bell et al. 2007). Ageing has been noted to reduce the LRP1-mediated

A β absorption into the blood (Bell et al. 2009). Apolipoprotein E (APOE) modulates this transendotelial clearance process of A β by being a ligand for LRP-1 (Kim et al. 2009, Castellano et al. 2011). The APOE is a major apolipoprotein in the brain, stabilizing the lipoproteins (Franceschini et al. 1996, Mahley et al. 2000, Mahley et al. 2016), participating in cholesterol and lipid transport, and being a component in lipoproteins (high and low density lipoproteins) and a ligand for LDL. In addition, it seems to have a role in synaptogenesis, neuroinflammation (White et al. 2001) and brain repair (Davies et al. 2014).

In contrast to LRP-1, RAGE-mediated transport of A β takes place on the luminal side of the blood vessels (BBB). RAGE mediates the influx of A β from the blood into the brain (Zlokovic 2002) and from the interstitial space into neuronal cells (in co-operation with LRP-1), thus having a role in eliminating A β at the capillary level (Zlokovic et al. 2004). A β deposition in the vessel wall has been thought to cause greater BBB permeability by promoting inflammation and the cytotoxicity reaction (Rocher et al. 2003, Carrano et al. 2011), and by the degeneration of vessel wall smooth muscle and endothelial cells, and pericytes (Erickson et al. 2013). BBB dysfunction has been noted to correlate with the occurrence of perivascular tau (Blair et al. 2015).

(3.) The perivascular drainage route at the capillary level has been thought to be the main clearance way for A β (Weller et al. 2008, Preston et al. 2003). However, it has been noted to be much slower than the clearance of A β by its absorption into the blood via LRP1 (Bell et al. 2007). Perivascular drainage has been noted to compensate for the transport of A β into blood clearance if the LRP mechanism is blocked (Shibata et al. 2000) or when the neprilysin enzyme levels in the brain are reduced (Miners et al. 2006).

Lymphatic drainage is driven by filtration pressure, contraction of adjacent muscles and the pulsation of neighbouring arteries. The motive force is related to a pulse wave travelling along arteries and a contrary wave drives the perivascular lymphatic drainage out of the brain (Schley et al. 2006). Soluble A β can diffuse into the extracellular space along the lymphatic drainage pathway in the walls of capillaries and arteries to the cervical lymph nodes (Carare et al. 2008, Weller et al. 2009). A β deposition in the small and medium-sized vessel walls has been thought to block the perivascular lymphatic drainage pathway (Carare et al. 2008, Weller et al. 2009) by stiffening the vessel walls. Similar stiffening of arteries with age and comorbid atherosclerosis would also reduce the amplitude of the pulse wave and contrary wave, and thus hinder or slow the periarterial lymphatic drainage and A β clearance from the brain (Schley et al. 2006, Weller et al. 2008).

According to a more recent study, a glial-dependent perivascular waste clearance “glymphatic” pathway of hydrophilic and lipophilic molecules is also the key contributor of soluble A β clearance (Iliff et al. 2012). Failure of that clearance might lead the amyloid plaque formation and AD progression (Iliff et al. 2012, Iliff et al. 2013, Plog et al. 2018, Smith et al. 2018).

2.3.3. Hypothesis on the pathogenesis of cerebral amyloid angiopathy

The mechanism and process of A β accumulation in cerebral vessel walls is complicated and not yet fully understood. There are diverse genetic, biochemical and metabolic factors involved in the process. In addition to the A β peptide, vascular amyloid deposition can also contain other peptides such as the APOE protein, α 2 macroglobulin and, LDL receptor-related protein (Revesz et al. 2003).

Various hypotheses on the origin of the vessel wall accumulation of A β have been presented.

- (1) The vascular theory underlines the local production of A β in the vessel walls. A β has been observed near the vessel wall (Frackowiak et al. 1994) and shown to initially appear in the basement membrane of the smooth muscle cells (Vinters et al. 1983, Vinters 1987). Smooth muscle cells are suggested to be the initial cause of the A β aggregates (Kalaria et al. 1996, Burgermeister et al. 2000).
- (2) The systemic theory (Zlokovic et al. 2002) supports the idea of A β in circulating or cerebrospinal fluids being the potential precursor of the vessel-wall-deposited amyloid.
- (3) The drainage hypothesis (Weller et al. 1998) postulates that a comorbid atherosclerosis or other vascular dysfunction might influence A β clearance by reducing the pulse amplitude of cerebral vessels and A β accumulation into capillary and artery vessel walls (Weller et al. 1998, Van Dorpe et al. 2000).

In recent studies based on mouse models, the neuronal origin of A β has been the main hypothesis explaining CAA (Burgermeister et al. 2000, Van Dorpe et al. 2000).

Accumulation of A β to arterial wall

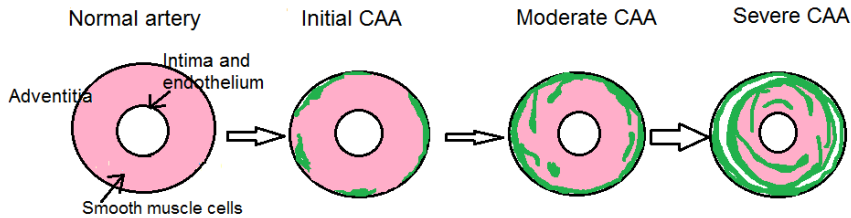


Figure 5. A β initially appears in the basement membrane around the smooth muscle cells in the outer region of the media near the adventitia (Vinters 1987b). A β deposition in the vessel walls is lumpy and segmental. Next, it is seen spreading in the media between the smooth muscle cells (Wisniewski, Wegiel 1994) and towards the internal elastic lamina of the arteries and the endothelium of arterioles. First, it causes thickening of the basement membrane, then it destroys the smooth muscle cells (Verbeek et al. 2000), replacing the smooth muscle layer (Holton et al. 2001, Revesz et al. 2003). In severe CAA, smooth muscle cells can be degenerated or lost completely, with fibrinoid necrosis and the development of microaneurysms. The vessel walls of the small arterioles and capillaries can be entirely replaced by amyloid apart from the endothelium. Modified from Thal et al., 2008.

2.3.4. Grading of cerebral amyloid angiopathy

Several grading systems have been described to evaluate the prevalence and severity of CAA. As there is variation in the number of brain areas evaluated, both the incidence and prevalence of CAA have varied between the studies (Attems et al. 2011). Currently, no standardised, widely accepted method exists for grading CAA. The two probably most commonly used methods are the systems described by Olichney (Olichney et al. 1995) and Vonsattel (Vonsattel et al. 1991). In addition to those two methods, Thal used a method assessing the distribution of CAA across the entire brain (Thal et al. 2003) and Attems a system that scored the meningeal and cortical blood vessels separately (Attems et al. 2005). Furthermore, Love et Chalmers (Love et al. 2014) published a

scoring scheme for the CAA grades, which also takes into account the presence of capillary A β as 0/1 (Table 6.).

Table 6. Some of the grading systems used for CAA

System	Blood vessel (BV) taken into account	Specific
Olichney scale (0-4)	0= no A β positive blood vessels (BV), 1= scattered A β positivity in either leptomeningeal or intracortical BV 2= strong circumferential A β positivity in either leptomeningeal or intracortical BV 3= widespread strong circumferential A β positivity in leptomeningeal and intracortical BV 4= 3+ additional dysphoric changes	
Vonsattel graded	Mild = amyloid is restricted to the tunica media, Moderate = tunica media is replaced by amyloid, Severe = extensive amyloid deposition, possible focal fragmentation and fibrinoid necrosis.	severity of CAA
Thal	Stage 1= CAA occurs only in neocortical areas, Stage 2= allocortical regions as well as the hypothalamus, the midbrain and the cerebellum are involved, Stage 3= CAA occurs also in basal ganglia, thalamus, white matter and/or brainstem	
Attems	Severity after Olichney.	scored separately in meningeal and cortical blood vessels
Love et Chalmers scoring	Scoring of grades 0-3, taking account of four regions: occipital, parietal, temporal and frontal and also capillary deposition.	taking into account the presence of capillary A β as 0/1

Olichney scale (Olichney et al. 1995). Vonsattel graded (Vonsattel et al. 1991). Dietmar Thal method (Thal et al. 2003). Johannes Attems system (Attems et al. 2005a). Love et Chalmers scoring (Love et al. 2014).

2.3.5. The prevalence and topography of cerebral amyloid angiopathy

A modest amount of A β in the brain vessel walls is a relatively common finding in the elderly, regardless of their cognitive status. The prevalence of CAA has been observed to increase with age in several studies (Vinters et al. 1983, Esiri et al. 1986, Yamada et al. 1987, Masuda et al. 1988, Xu et al. 2003). In most studies on hospital-based cohorts, the prevalence of CAA has varied within the

range 36%-68.4% (Esiri et al. 1986, Yamada et al. 1987, Vinters 2001, Attems et al. 2005, Attems et al. 2007).

The following population-based studies have found the prevalence of CAA to vary between 22.8%-48.6%: The Japanese Hisayama Study (Masuda et al. 1988), the Honolulu-Asia Aging Study (HAAS) (Pfeifer et al. 2002), the Medical Research Council Cognitive Function and Ageing Study (Neuropathology Group. Medical Research Council Cognitive Function and Ageing Study 2001), the Cambridge City over 75 Cohort Study CC75C (Brayne et al. 2009) and the Adult Changes in Thought (ACT) study (Sonnen et al. 2007, Arvanitakis et al. 2011b). In one community-based cohort, the prevalence was as high as 84.9% (Arvanitakis et al. 2011b).

Nevertheless, the occurrence of CAA is in most cases mild, as CAA can be seen in a focal patchy pattern in diverse brain regions. CAA first appears at the neocortical layers (Thal et al. 2003) and has been noted to be more abundant in the meningeal than cortical vessels (Attems et al. 2007). In a hospital-based cohort, CAA was shown to be most common in the frontal, parietal and temporal lobes (Ellis et al. 1996, Vinters et al. 1983). In a Japanese population-based study, CAA was most prevalent and severe in the frontal, followed by the parietal lobe (Masuda et al. 1988), but in contrast to this, the HAAS study reported the highest frequency of severe CAA in the occipital lobe (Pfeifer et al. 2002). The occipital lobe has also been noted to be primarily affected in the study by Yamada and co-workers (Yamada et al. 1987), and AD patients have been shown to develop CAA most commonly in the occipital lobe (Tian et al. 2003).

2.3.6. Association of cerebral amyloid angiopathy with dementia

As long ago as 1986, Esiri noted that demented individuals more frequently had severe CAA as the non-demented (Esiri et al. 1986). This finding has been confirmed in some population-based or longitudinal studies, such as CFAS (Neuropathology Group. Medical Research Council Cognitive Function and Ageing Study 2001) and CC75C (Cambridge City over 75 cohort) (Xuereb et al. 2000). In the CFAS study, the burden of CAA associated with dementia significantly and independently (Neuropathology Group. Medical Research Council Cognitive Function and Ageing Study 2001). In one study, CAA and senile plaques were noted to have an inverse association (Tian et al. 2003) while in some others, a significant positive relationship was reported (Thal et al. 2003, Attems et al. 2005). CAA has been detected in over 80% of the AD patients in various cohorts (Esiri et al. 1986,

Yamada et al. 1987, Ellis et al. 1996, Yamada et al. 2002, Attems et al. 2007). It therefore has been suggested to have an essential role in the pathogenesis of AD (Nicoll et al. 2004).

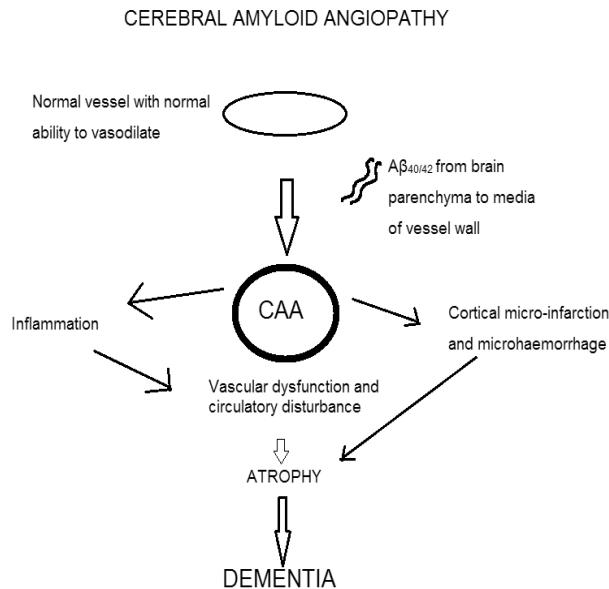


Figure 6. Hypothesis of the consequences of CAA. CAA is thought to cause weakening of the vessel wall, leading to a possible haemorrhage or local infarction. In addition, CAA-related inflammatory reaction and accumulation of monocytes and macrophages near the vessel structure can increase vascular dysfunction and circulatory disturbance leading to neuronal death, atrophy and possible cognitive impairment and dementia. Partly modified from Smith et al. 2018.

CAA has been regarded as a rare but important cause of intracerebral haemorrhage (ICH) in the aged (Jellinger et al. 1977). The prevalence of severe CAA and lobar ICH has been shown to be associated in some meta-analysis studies (Samarasekera et al. 2012). However, not all studies have shown a strong connection between CAA and ICH (Attems et al. 2008). The CAA-associated ICH might not be lethal, but one third of the CAA-associated ICH has been estimated to recur during the first year (Hirohata et al. 2010). Nevertheless, severe CAA has been shown to be associated with haemorrhages (Ellis et al. 1996, Attems et al. 2008), and haemorrhagic strokes (Kalaria 2003).

2.3.7. Capillary amyloid angiopathy

In addition to general small and middle-sized vessel CAA, A β accumulates also at the capillary (Figure 7) basement membrane as small bumps representing capA β consisting of A β ₄₂ and partly A β ₄₀ (Figure 8) (Attems et al. 2004b, Jaynes et al. 2006, Oshima et al. 2006, Richard et al. 2010).

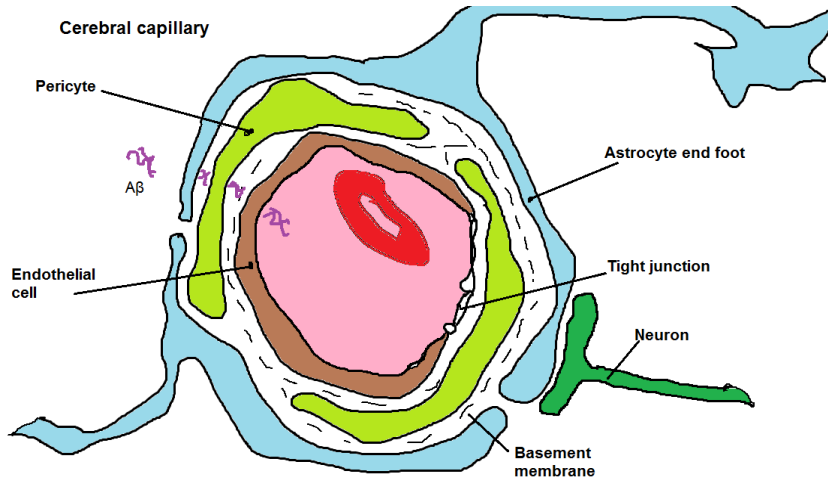


Figure 7. The capillary vessel wall forms the BBB, the border between the brain parenchyma and blood circulation. The capillary wall consists of the basement membrane, pericytes and the endothelium. The endothelial cells function as the barrier by regulating protein and fluid transport by tight junctions and receptor-mediated transport (Abbott et al. 2006). Pericytes, located between the endothelium and end foot of neurons affect the structural stability of the vessel walls and control cellular contraction/relaxation, affecting the blood flow in capillaries. They also clear toxic products from the CNS (Peppiatt et al. 2006, Sagare et al. 2013). Proper function of the capillary wall is essential for the viability of neurons at the brain parenchyma nearby. Figure modified from Zenaro et al. 2017.

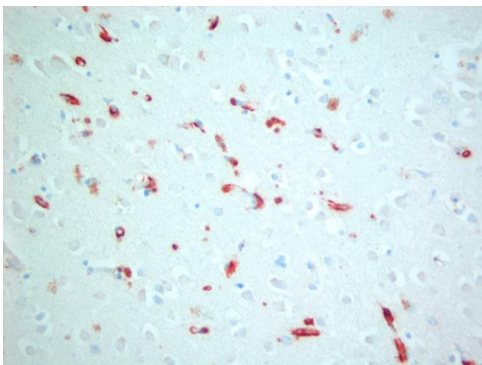
A β deposition in the cerebral vessels has been stated to associate with pericyte degeneration (Verbeek et al. 2000). AD patients have been shown to suffer from a significant loss of pericytes in the cortex and hippocampus compared to control subjects, correlating with the severity of BBB degradation (Sengillo et al. 2013). Pericyte dysfunction has been shown to be associated with the AD neuropathology (Bell et al. 2010, Zlokovic 2011, Sagare et al. 2013, Sengillo et al. 2013, Winkler et al. 2014, Montagne et al. 2015,); thus, the role of the capillary involvement of A β may be considerable in the progress of AD.

2.3.7.1 Cerebral amyloid angiopathy Type 1 and Type 2

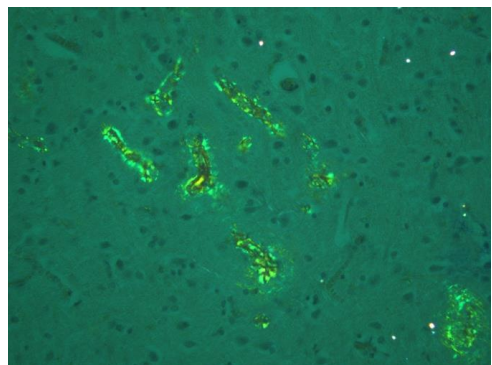
It has been suggested that CapA β deposition at the cerebral cortex divides CAA morphologically into two distinct types, CAA-Type1 with capA β and CAA-Type2 without it (Thal et al. 2002a). CapA β deposition is shown to occur in the same brain regions as general CAA (Thal DR et al. 2008b), the predilection sites being cortical layers III-IV (Oshima et al. 2006), layers II-V of the neocortex (Thal et al. 2002a), the subiculum CA1 region, the entorhinal cortex, and the occipital cortex (Thal et al. 2008b).

The chronological order of A β accumulation in large vs smaller vessel walls is still somewhat unclear. It is not known whether the accumulation is synchronous in both capillary and arterial walls or if one is preferred to the other. However, capA β can occur with a relatively scanty large vessel CAA (Richard et al. 2010), possibly indicating insufficient clearance of A β specific to the BBB in the capillaries (Richard et al. 2010).

However, the severity of the general CAA and the presence of capA β have been found to correlate (Attems et al. 2004a, Richard et al. 2010), and capA β has been considered to represent an indicator of a high-grade CAA (Attems et al. 2004b). A β deposition in small arterioles has been believed to represent the end stage of the most severe CAA (Olichney et al. 2000), but Thal's study on CAA Types indicates that CAA with capA β (CAA-Type1) is unlikely to be the late stage of CAA without capA β (CAA-Type2) (Thal et al. 2002a). Instead, they seem to represent two different entities.



a. Immunohistochemical staining



b. Congo-red staining

Figure 8. CapA β . (A) Severe capA β in immunohistochemical A β staining. (B) A Congo-red staining of severe capA β (400-fold magnification).

CapA β has been noted to be associated significantly with AD-type neuropathology (Attems et al. 2004a, Attems et al. 2010) and clinical AD (Thal et al. 2008a).

Near the capillary structures, there are also parenchymal A β deposits at the glia limitans immediately beside the cortical capillary construction, named pericapillary A β (pericapA β), consisting mainly of A β_{42} (Attems et al. 2010). These changes were previously classified as capillary CAA (Attems et al. 2004a) and occasionally defined as "dyshoric angiopathy". The pericapA β deposition has been thought to represent a pathogenesis distinct from capCAA, probably being an early form of A β deposition (Attems et al. 2010).

2.3.8. Genetics of cerebral amyloid angiopathy

CAA with capA β deposition (CAA-Type1) has been shown to be associated more frequently with the AD-related genetic risk locus, the *APOE* $\epsilon 4$ allele, than CAA without capA β (CAA-Type2) (Thal et al. 2002a, Richard et al. 2010). An increased number of the $\epsilon 4$ alleles of *APOE* has even been shown to influence the severity of capA β findings (Richard et al. 2010). In contrast to this, CAA-Type2, unlike CAA-Type1 or controls, has been shown to be frequently associated with the *APOE* $\epsilon 2$ allele (Thal et al. 2002a). The copy number variation or locus duplication of A β PP can lead to significant A β deposition, dementia and possible CAA, and six specific mutations (*A692G*, *E693Q*, *E693G*, *E693K*, *N694D*, *L705V*) to severe CAA (Rovelet-Lecrux et al. 2006, Revesz et al. 2009).

2.3.9. Cerebral amyloid angiopathy and inflammation

There can be inflammation associated with CAA. According to some studies, CAA-related inflammation can be divided into two partly overlapping types of inflammation: (1.) the perivascular-non-vasculitis type with perivascular multinucleated giant cells, and (2.) the vasculitis-type with transmural granulomatous angitis in vessel walls (Eng et al. 2004, Scolding et al. 2005) with subacute leukoencephalopathy. In addition, monocytes and macrophages can accumulate in CAA-affected vessel walls (Yamada et al. 1996).

2.4. The other dementias

2.4.1 Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is thought to be the third most common dementia disorder after AD and VaD, representing about 20% of all dementias. DLB is defined as a progressive dementia disorder resulting in significant social and occupational functional impairment, often combined with fluctuating cognition, recurrent well-formed visual hallucinations and spontaneous features of Parkinsonism (McKeith et al. 2005). The first ordinary consensus guidelines for the neuropathological diagnosis of diffuse neocortical DLB require a combined neuron loss with Lewy-bodies (LB) at the brainstem (substantia nigra), limbic regions and cortex (McKeith et al. 1996). These intraneuronal Lewy-body inclusions consisting of alpha synuclein (α S) are detected semi-quantitatively with α S immunohistochemistry (McKeith et al. 2005). In addition to LB, Lewy neurites (α S immunoreactive neurites) and diffuse cytoplasmic immunoreactivity against α S can exist. At present, the recommendation is for the DLB pathology to be classified as follows: None, brainstem-predominant, limbic, neocortical-diffuse, amygdala-predominant (McKeith 2006, Hyman et al. 2012).

In Finland, the DLB prevalence has been reported to be similar (33.3/1000) (Rahkonen et al. 2003) than in the meta-analysis based on twenty-two studies in MEDLINE and EMBASE databases (0.02-33.3/1000) (Hogan et al. 2016). In the meta-analysis, the incidence reported was 0.5-1.6/1000 per year (Hogan et al. 2016).

2.4.1.1. Lewy-related pathology and cerebral amyloid angiopathy

The ADRP (NPs and NFTs) often coexists with DLB (McKeith et al. 1996). Pure DLB with no or a low level of ADRP is relatively rare, especially in older individuals (Hyman et al. 2012). Instead, DLB is frequently detected with a moderate to severe ADRP (Hamilton et al. 2000). It has been noted that demented persons with the LB pathology have coexisting AD, often a Braak-type pathology (Schneider et al. 2007). Where some population-based studies have found α S changes to be more frequent with NPs, no correlation has been found with the severity of NFT (Braak stage) (Mikolaenko et al. 2005). Nevertheless, the Lewy-related pathology is a relatively common finding in the elderly, and some population-based studies, such as the CFAS and Rush Memory study, have observed LB as being equally common in demented and non-demented individuals (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001, Schneider et al. 2007).

2.4.2 Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is a group of disorders with a varied clinical picture, including difficulties in personality and speech, and late parkinsonism-like motor problems. In most

cases, the lesions are located in the frontal and temporal lobes. The frontotemporal type of dementia (FTD), today included in FTLD, and argyrophilic cytoplasmic inclusions in neurons were first described by Arnold Pick in 1892.

The diagnostic criteria of neuropathological and clinical FTD were settled in 1994 (Anonymous 1994). In 2011, a new clinical classification of FTLD was introduced, dividing it into a behavioural variant and three primary progressive aphasia variants (non-fluent/agrammatic, logopenic and semantic) (Gorno-Tempini et al. 2011, Rascovsky et al. 2011). The prevalence of FTD has been estimated to be 15-22/100 000 (Knopman et al. 2011). The prevalence of FTD in Northern Finland has been estimated to be about 20.5/100 000 and the incidence about 5.54/100 000 (aged 45-65) (Luukkainen et al. 2015). The incidence of FTD has been estimated to be 2.7-4.1/100 000 (individuals <70 years) (Onyike et al. 2013).

The neuropathological diagnosis of FTLD requires an examination of neuronal loss, microvacuolisation, gliosis and spongiosis in the frontal and anterior temporal lobes and cingulate and insular cortex (Rosen et al. 2002). Protein inclusions, such as tau, TDP-43 or Fused in sarcoma - Ewing's sarcoma - TATA-binding protein-associated factor 15 (FET)-protein family accumulation in neurons can also be detected. Those immunohistochemical inclusion findings divide FTLD into four distinct neuropathological disorders; FTLD-TDP, FTLD-tau, FTLD-FET and the others (MacKenzie et al. 2016). In any clinical form of FTLD can appear with any of four neuropathological findings (MacKenzie et al. 2010, MacKenzie et al. 2016).

2.4.3 Other age-related dementias

A fairly new group of neurodegenerative dementias is Hippocampal sclerosis (HS) (Dickson et al. 1994). HS is mainly defined as pyramidal cell loss and gliosis in CA1 and the subiculum of hippocampus and hippocampal or extrahippocampal TDP-43 immunoreactive inclusions (Amador-Ortiz et al. 2007).

2.4.4 Vascular dementia

2.4.4.1. Definition

Vascular dementia (VaD) has been regarded as the second most common dementia after AD.

VaD (Fisher et al. 1968), also called vascular cognitive impairment (VCI) (Rockwood et al. 2007), has been defined as a dementia which is caused by problems in the blood supply of small or large brain vessels leading to an ischemic brain parenchymal lesion and cognitive decline (Jellinger 2007).

Vascular brain syndromes have been divided into small vessel disease (SVD), large vessel disease (LVD), and multi-infarct dementia.

2.4.4.2. Criteria for vascular dementia

There are currently no widely accepted and well-validated clinical diagnostic criteria for VaD, apart from some specific types of hereditary genetically-defined small vessel diseases, such as CADASIL and Swedish hereditary multi-infarct dementia. However, some sets of criteria have been developed, such as the Hachinski Ischemic Score (Hachinski et al. 1975), DSM III (APA, 1980), DSM III-R (APA, 1987), ICD-10, DSM-V (2013) and VASCOG (The international Society for Vascular Behavioral and Cognitive disorder) and the most commonly used DSM-IV and NINCDS-AIREN criteria. There are also the following criteria for mild cognitive impairment or dementia caused by vascular changes defined by the American Heart Association (AHA), American Stroke Association (ASA) (Gorelick et al. 2011), the Alzheimer's association and the American Academy of Neurology (AAN):

- (1.) The diagnosis of mild cognitive impairment or dementia is confirmed by neurocognitive testing, including judgment, planning, problem-solving, reasoning and memory.
- (2.) Imaging evidence of changes in the brain vasculature, recent stroke or other blood vessel change.
- (3.) No evidence of other factors contributing to cognitive decline.

2.4.4.3. Risk factors for vascular dementia

The risk factors for VCI and VaD are mostly identical to those for stroke (Gorelick et al. 1993). Those risk factors can be divided into four classes; demographic (age, male sex, low education), atherosclerotic (hypertension, smoking, hyperlipidemia), genetic (familial as CADASIL or *APOE ε4*) and stroke-related (tissue loss, cerebral strategic infarction) (Gorelick et al. 2004).

2.4.4.4. Neuropathology of vascular dementia

Unfortunately, no widely accepted and validated neuropathological criteria exist for VaD. In a neuropathological examination, white matter lesions with lacunar infarctions, varying size of cortical infarcts, micro-infarcts and micro-bleeds can be detected. In the neuropathological examination, the infarcts are classified according to the location (lobar, cortical or white matter) and macroscopic or microscopic size. In some studies, standards of guidelines of vascular lesion have been settled (Hachinski et al. 2006) and update (Deramecourt et al. 2012).

2.4.4.5. Epidemiology of vascular dementia

VaD, the most severe form of VCI (Wiesmann et al. 2013), has been proposed to be the second most common cause of dementia in the elderly. Due to the lack of clinical and neuropathological consensus criteria for VaD, the prevalence and incidence rates are variable. In clinical trials, the prevalence has been estimated to be 15-20% (Lobo et al. 2000, Dubois et al. 2001, Bowler et al. 2007).

The incidence of VaD is dependent on the age of the study cohort (Fratiglioni et al. 2000) and has been estimated to range from 2.52 (Hebert et al. 2000) to 3.8 (> 65 years) per 1000 person-years (Bowler 2007). The incidence in very elderly males has been reported to be 15.9 (>90 years) and females 9.3 (>85 years) per 1000 person-years (Bowler et al. 2007). The incidence of pure VaD, without any other neuropathology, may be higher among the younger demented people (von Strauss et al. 1999, Borjesson-Hanson et al. 2004) than the oldest old (Knopman et al. 2003, Vinters et al. 2000), who suffer more from mixed dementia (Kalaria et al. 2000). Small vascular changes are common in the elderly, one third of whom suffer from micro-infarcts, as noted in population-based studies (Arvanitakis et al. 2011), and two thirds from micro-bleeds or haemorrhages (Fisher et al. 2010). Large haemorrhages are rarer, affecting about 6.5% of the population (Masuda et al. 1988). In some population-based studies, VaD has appeared as common as AD (White et al. 2002). In addition, the combination of VaD with a varying amount of AD-type pathology is typical (White et al. 2002). In reality, a pure isolated vascular sporadic disease has been demonstrated to be a relatively uncommon finding in demented individuals (Jellinger et al. 2010).

2.5. Dementia based on mixed pathology

In younger patients, the specific clinical and neuropathological findings of each dementia syndrome are often quite obvious. In contrast to this, the setting of an accurate dementia diagnosis in the elderly individuals is much more complicated.

One reason for those complications is the high prevalence of multiple brain pathology in the elderly, as shown in the many population- or community-based neuropathological studies, both in demented and non-demented individuals (Schneider et al. 2007, Kawas et al. 2015). The neuropathological changes become more severe through ageing. The population- or community-based neuropathological studies have shown that pure forms of the AD-, VaD-, or LB-type neuropathology are quite rare, especially among the very elderly (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001, White et al. 2005, Schneider et al. 2007). In the oldest old (in the 90+ study), one third of the individuals had two or more types of neuropathological findings

(Kawas et al. 2015). Multipathology has been noted to increase the risk of dementia threefold if more than one neuropathological variable is present (Schneider et al. 2007).

AD has been regarded as the most common dementia, mainly based on hospital-based cohorts. However, it has been suggested that the VaD-type pathology applies to most of the elderly AD patients (Fernando et al. 2004, Schneider et al. 2007). In addition, two thirds of the elderly AD patients have been shown to have a concomitant LB pathology (Wang et al. 2012, Massoud et al. 1999). The LB and VaD-type pathologies have been observed to have the strongest effect on the cognition of an AD patient (Montine et al. 2009, Nelson et al. 2010). In addition to LB and vascular brain injury, HS commonly appears with AD (Hyman et al. 2012).

Concomitant TDP-43 pathology has been shown to have a strong effect on cognition, memory loss and medial temporal atrophy, not mediated by HS, in AD (Josephs et al. 2014). TDP-43 inclusions have been detected in some studies in 23% of AD cases (Amador-Ortiz et al. 2007), whereas in other studies as much as in 36-56% (Arai et al. 2009) to 57% (Josephs et al. 2014) of AD cases. TDP-43 positive subjects have been noted to be tenfold more likely to be cognitively impaired compared to TDP-43 negative subjects (Josephs et al. 2014).

2.6 The role of population- or community-based studies in neuropathological research

There are more than ten recent population- or community-based neuropathological studies on the neurodegenerative diseases leading to dementia (Table 7). These studies vary concerning the size of cohort, gender, age of participants, and the clinical and neuropathological variables examined.

The population-based approach affords the best chance of comparing the diversity of neuropathological lesions in elderly individuals without taking into account the clinical status. They can provide information on the distinction between the normal effect of ageing and the development of cognitive decline or dementia. For example, large population-based studies such as the MRC-CFAS (Neuropathology Group of the Medical Research Council Cognitive Function and Aging Study 2001) and CC75CC (Xuereb et al. 2000) brought up the significance of CAA in the pathogenesis of dementia.

Table 7. Population- or community-based or longitudinal studies on dementia with clinical and neuropathological data with possible genetic data

Study	N	Age	Demented %	CAA	CapAb	NP/ CERAD	NFT/ Braak	LB	MI/Inf	APOE ϵ 4	Limitation
ACT	221	>65		+		+	+	+	+	+	Urban population
BLSA	117					+	+	+			
CC75C	456	>75		+		+	+	+	-/+	-	>75 years
Haas	285	>71		+	+	+	+	+	+	+	Only male
Hisayama Study	400	>65		+		+	+	+			
MRC-CFAS	209	70-103	48%	+		+	+	+			
Nun study	146					+	+				Only female
OPTIMA	101					+	+	+		+	
ROS	214					+	+	+			
Rush Memory	141		35.5%			+	+	+	+		
Vantaa 85+		>85		+	+	+	+	+	+	+	

N (Number of Autopsies) CERAD= the Consortium to Establish a Registry for Alzheimer disease, M= moderate frequency of neuritic plaques, F= frequent neuritic plaques. Braak stage (0-II) versus (IV-VI). CAA= mean percentage of subarachnoid and cortical non-capillary blood vessel with cerebral amyloid angiopathy in six samples. CapA β b: capillary amyloid angiopathy. APOE ϵ 4: carriers of the APOE ϵ 4 allele.

ACT (Adult Changes in Thought: King county), USA; Washington; (Sonnen et al. 2007)

BLSA (Baltimore Longitudinal Study on Ageing) (Troncoso et al. 1998, Mikolaenko et al. 2005)

CC75C (Cambridge City over 75 Cohort), UK (Xuereb et al. 2000) (Brayne et al. 2009)

Haas (The Honolulu-Asia Aging Study); USA (Pfeifer, White et al. 2002) (Launer et al. 2008)

Hisayama Study (Japan); (Masuda J, 1988)

MRC-CFAS (The MRC Cognitive function and Ageing Study) England and Wales (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001)

Nun Study (Riley et al. 2002, Snowdon et al. 1997)

OPTIMA (Oxford Project to Investigate Memory and Ageing) (Jobst, et al. 1997)

ROS (Religious Orders Study) Roman Catholic clergy (Arvanitakis et al. 2011)

Rush Memory and Ageing Project, Chicago (Schneider et al. 2007)

Vantaa 85+ (Tanskanen et al. 2012, Makela et al. 2016, Tanskanen et al. 2017)

3. AIMS OF THE STUDY

The general aim of the study was to clarify the vascular and neurodegenerative pathologies underlying dementia in a very elderly population.

The specific aims were:

- 1) To investigate the frequency and severity of general CAA in a very elderly population.
- 2) To investigate the frequency and severity of capA β and its association with AD neuropathology, *APOE* ϵ 4 and dementia.
- 3) To investigate the effect on clinical dementia of several types of neurodegenerative and vascular pathologies and their combinations.
- 4) To investigate associations between the genetic risk loci for AD and the different neurodegenerative features of AD (NPs, NFTs, CAA and capA β).

4. MATERIALS AND METHODS

4.1 Subjects

This study is part of the prospective population-based Vantaa 85+ human autopsy study, which includes 601 individuals living in the city of Vantaa on April 1, 1991, aged 85 years or older. 553 subjects were clinically examined by a neurologist. Clinical follow-up evaluations were performed in 1994, 1996 and 1999 and 2001, where possible.

Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, revised third edition, (DSM III-R; American Psychiatric Association, 1987). The dementia diagnosis was based on a clinical examination, Mini-Mental State Examination, MMSE (Folstein et al. 1975), and required the consensus of two neurologists. It was required that the dementia diagnosis was made more than three months prior to death. 195 of 300 autopsied study subjects were demented (Tanskanen et al. 2017).

The presence of hypertension (N=299) was based on the use of blood pressure-lowering medication in the clinical examination. Peripheral blood samples were used for measuring the cholesterol and triglyceride levels (N=262) by standard biochemical methods (Mylykangas et al. 2001).

There were a total of 306 autopsied subjects (79.5% female) from 85 to 105 age at death, mean 92±3.7 years.

4.2 Neuropathological examination

The brains were fixed in 4% formaldehyde for at least four weeks. Specimens from six brain regions were taken according to the standard protocol.

4.2.1 Alzheimer's disease and Lewy-related pathologies

The ADRP (Braak stages and CERAD scores) was evaluated before the start of this thesis project by other medical practitioners (Polvikoski et al. 1995, Mylykangas et al. 1999), following the previously published guidelines (Mirra et al. 1991, Braak, Braak 1991).

In Studies II and III, we compared the NP category 'no to moderate' (CERAD scores 0+S+M) with the NP score 'frequent' (CERAD score F) and the minor NFT pathology (Braak stages 0-IV) with the severe NFT pathology (Braak stages V and VI).

In Study IV, the occurrence of the NP score 'frequent' (CERAD score F) was compared with 'no NPs' (CERAD score 0). Severe NFT (Braak stages IV and VI) was compared with no or hardly any NFT pathology (Braak stages 0-II).

The Lewy Body (LB) –related pathology was estimated as described previously (Oinas et al. 2009), with ICH against α S clone 42. In Study II, the subjects with neocortical LB –related pathology were compared with controls (individuals with no LB-related pathology at the brainstem or limbic regions).

4.2.2. Cerebral infarcts and haemorrhages

The presence of cerebral infarcts, micro-infarcts or micro-haemorrhages was evaluated for Studies II and III. The presence of large (> 15 mm) and small (2-15 mm) cortical infarctions was estimated at autopsy (Mylykangas et al. 2001). Micro-infarctions (MI) were defined as focal star-like lesions of <2mm with neuronal loss and cystic tissue necrosis with surrounding foamy macrophages and a glia cell reaction in the H&E stained tissue sections in all six brain regions. Brain haemorrhages were classified as microscopic (<2 mm) or macroscopic. Micro-haemorrhages (MH) were evaluated for the presence of even small intracellular Prussian blue staining, and were estimated in all six brain regions.

4.2.3 Cerebral amyloid angiopathy

Six formalin-fixed, paraffin-embedded tissue sections, including the leptomeninges, were taken from each subject for analysis of CAA and $\text{capA}\beta$.

The specimens were from the frontal lobe (right medial frontal gyrus), parietal lobe (inferior parietal lobule), temporal lobe (medial temporal gyrus), occipital cortex (left occipital primary visual cortex), hippocampus (hippocampal formation, entorhinal and transentorhinal cortices and occipitotemporal gyrus) and cerebellum (right parasagittal superior region with dentate nucleus).

The prevalence and severity of CAA in the middle-sized and large meningeal and cortical blood vessels was estimated using histologically modified Puchtler's alkaline Congo red staining applied in eight- μm -thick tissue sections analysed under polarized light. The Congo-red-positive samples in Study I and all the samples (from the each six brain regions) in Study II were analysed also with immunohistochemistry (IHC). For IHC, the six- μm -thick paraffin sections were deparaffinised and pre-treated with 0.5% H_2O_2 for 30min and then 100% formic acid for 5min, followed by an overnight incubation with a primary antibody (Mouse anti-beta amyloid clone 4G8, residues 17-24). The

immunoreactivity was detected using the avidin-biotinylated HRP complex (ABC) system (Vector Lab, CA, USA).

For Studies I, II, III and IV, the severity of CAA was estimated as a percentage of Congo red or IHC-positive blood vessels of the entire area of the specimens. The meningeal and cortical vessels were evaluated separately. In addition to this, the total index of CAA severity was defined by counting the percentage of meningeal and cortical vessels in all six brain areas and dividing the sum by six.

4.2.4 Capillary amyloid β

For Studies II and IV, the presence of capA β was analysed in the same six brain regions as CAA (frontal, parietal, temporal, occipital cortex, hippocampus and cerebellum) using IHC as described above (mouse anti-beta amyloid clone 4G8, residues 17-24) independently of clinical data or the data on CAA severity or other neuropathological data. In 16 samples (from nine subjects) with weak A β IHC staining results, the diagnosis was based on the Congo red stain. In the hippocampal area, the results referred to findings in both the Ammon's horn (Cornu Ammonis, CA) and subiculum, but, in addition, the presence of capA β was separately evaluated in the hippocampus proper (the CA4-CA1 regions). We performed the diagnosis of capA β as described by Thal and Attems and others (Thal et al. 2002a, Attems et al. 2010). Only clear and obvious lumpy globular capillary wall depositions were included. The pericapillary parenchymal A β deposition was excluded. The presence A β deposition in capillaries (yes /no) was analysed in the whole tissue slices, using x 400 magnification (HPF). The severity of capA β was graded as previously described (Attems et al. 2004a): 0, no affected capillaries; 1, less than one affected capillary/HPF; 2, one to two affected capillaries/HPF; 3, more than two affected capillaries/HPF. Grade 1 capA β /1HPF was defined as mild and grade 2-3 capA β /1HPF as severe.

Multiple capA β was defined as capA β deposition in more than one brain region. Subjects with simultaneous severe (grade 2-3) and multiple (more than just one brain region) capA β deposition, were described here as severe-multiple-capA β .

The term 'CAA-Type1' was used for subjects having even a single A β positive capillary in any brain region (Thal et al. 2010), with or without CAA. Subjects with CAA-Type2 were defined as CAA without capA β deposition in any of the brain regions investigated. Subjects without positivity for A β IHC or Congo red in blood vessels of any size were defined as non-CAA controls.

4.2.5 Statistical analyses of neuropathological variables

The statistical analyses in Studies I, II and III were performed using the SPSS for Windows versions 17, 18, 19 and 20 software. The *P*-value <0.05 was considered significant.

In Study I, differences in the prevalence of CAA between the six brain regions were analysed using the Wilcoxon sign-rank/matched pair test or McNemar's test, and the difference between the study groups using the Mann-Whitney U-test or χ^2 -test. The correlation between the severities of meningeal and cortical CAA in the six brain regions was analysed by the Spearman correlation analysis. Logarithmic analyses were used for the percentage values of meningeal and cortical CAA and logistic regression analysis to study the association of CAA with gender and age.

In Study II, the comparison of dichotomous variables (gender, dementia, occurrence of severe CERAD score or Braak stage) and the distributions of the *APOE* genotypes (see methods 4.3.1) across the CAA-Types were performed by the Chi-square (χ^2 -test). Spearman's correlation tests of nonparametric correlation were used in order to compare the CAA types with other neuropathologies, the *APOE* genotype and dementia. The non-parametric Mann Whitney U test was used for comparing independent variables without normal distributions. Binary logistic regression analyses were used to estimate the association of CAA-Types with the neuropathological variables controlling age and gender. The odds-ratios (OR) were obtained with 95% confidence intervals (CI).

In Study III, logistic regression analysis was used to study the associations between different neuropathologies and dementia, and the correlations between the neuropathologies (CERAD, Braak, CAA, infarcts and haemorrhages, neocortical LB-related pathology) and the *APOE* $\epsilon 4$ allele status were analysed using the Spearman bivariate correlation analysis. The variance in eight quantitative variables (NFTs, senile plaques, hemispheric and deep macroscopic infarcts, cortical micro-infarcts of <2 mm, cortical micro-haemorrhages (MH), and the severity of CAA and neocortical LBs) were analysed using factor analysis with the rotation method and illustrated in a three-dimensional form. The statistics of Study IV are described below.

4.3. Genetic analyses

4.3.1 Candidate gene approach of *APOE*

In Study II, *APOE* genotyping was performed by analysing the candidate gene polymorphism by PCR as described previously (Myllykangas et al. 1999). DNA was extracted from peripheral blood cells of 278 of the 300 neuropathologically examined study subjects (Myllykangas et al. 1999).

4.3.2. Evaluation of the Alzheimer's disease risk loci

In Study IV, we used GWAS data generated previously (Peuralinna et al. 2015) by Infinium Human370 BeadChips (Illumina, San Diego CA) for 327 521 variants of 512 participants. The data quality control was performed by a standard PLINK v1.9 (Purcell et al. 2007) protocol (Anderson et al. 2010). In the quality control, all cases with any qualitative challenges were excluded.

A PubMed search was performed to identify all the loci that have been reported in previous GWAS analyses of samples from participants with clinically and/or neuropathologically diagnosed AD. In addition to *APOE*, we found reports on 44 variants at 29 loci. Variants of genes near these candidate loci were extracted from a quality controlled genome-wide SNP array. To cover nearby variants of possible interest, variants within 1kb of each candidate gene were also included in the study. The SNP panel did not include any markers in three of the risk loci Triggering Receptor Expressed on Myeloid cells 2 (*TREM2*) and Major histocompatibility complex, class II, DR beta1 (*HLADRB1*) and Exocyst complex component 3-like 2 (*EXOC3L2*).

In order to obtain more thorough information on the variation at the whole-genome level, all the Vantaa 85+ genetic data (n=512) were imputed. The GWAS genotypes were compared with the genotypes of a 286-individual previously sequenced subset of the whole-genome data of Vantaa85+. Imputation was performed for the same 44 candidate genes as were used in the SNP analysis. Imputation was performed using IMPUTE2 (Howie et al. 2009), and the 1000 Genomes phase3 data (October 2014 release) supplied by IMPUTE2 was used as the reference panel.

4.3.3 Statistical analysis of the genotype data

In the analyses of Study IV, the severe AD-type data were compared with the category “no or hardly any AD neuropathology”. The occurrence of ‘severe NPs’ (CERAD score M-F) was compared with ‘no NP’ (CERAD score 0). ‘Severe NFT’ (Braak stages IV and VI) was compared with ‘no or hardly any NFT pathology’ (Braak stages 0-II). CAA and capA β were analysed as in previous works, described above (CAA as a percentage of affected vessels analysed as a continuous variable and capA β as present or absent).

The association analyses between the *APOE* $\epsilon 4$ allele and neuropathological variables were performed using logistic (Braak, CERAD, capA β) or linear (CAA) regression analysis with age and sex as covariates.

For the SNP array data, the statistical analyses of the 341 markers (of the panel) were performed using PLINK. Case-control association tests were calculated using both the allelic chi-square test and logistic regression (multiplicative model). Quantitative trait associations were calculated using the asymptotic Wald test and linear regression. The analyses for each risk locus were performed with or without the *APOE* $\epsilon 4$ status as a covariate. Age and sex were used as covariates in all analyses. The value $p < 0.05$ was considered significant.

4.4. Approval for study

The Vantaa 85+ study was approved by the Ethics Committee of the Health Centre of the City of Vantaa and by the Coordinating Ethics Committee of the Helsinki University Central Hospital. The Finnish Health and Social Ministry approved the use of the health and social work records, and death certificates. Blood samples were collected only after the subjects or their relatives gave informed consent. The National Authority for Medicolegal Affairs (VALVIRA) approved the collection of tissue samples at autopsy as well as their use for research. A written consent for autopsy was obtained from the closest relatives.

5. RESULTS and DISCUSSION

5.1 Frequency and distribution of cerebral amyloid angiopathy (I)

Our study shows that CAA is very common in the elderly, but in most cases the severity of CAA is modest. In our cohort, CAA was most prevalent in the parietal lobe and most severe in the frontal lobe.

(1.) Unfortunately, there are no widely accepted grading systems for evaluation of the presence and severity of CAA, and so various grading systems from various brain regions have been used (Vonsattel et al. 1991, Olichney et al. 1995, Thal et al. 2003, Attems et al. 2005, Love et al. 2014).

We chose to analyse the percentage value of CAA-affected vessels from all small and mid-sized vessels, and separately evaluated six brain areas, as well as meningeal and cortical vessels. Consequently, comparison of the results between the different studies is challenging.

(2.) A certain degree of CAA was detected in 69.6% of our cohort, showing that CAA is a common phenomenon in the very elderly. In population-based studies, the prevalence of CAA has varied from 22.8% to 48.6% (Masuda et al. 1988, Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001, Pfeifer et al. 2002, Brayne et al. 2009). The highest prevalence of CAA, 84.9%, was observed in the Religious Order study (Arvanitakis et al. 2011b). In hospital-based studies, the prevalence of CAA has varied within the range of 36%-68.4% (Esiri et al. 1986, Vinters 2001, Yamada et al. 1987, Attems et al. 2005, Attems et al. 2007). Compared to the other population-based studies, the high age of our very elderly (85+) cohort may explain the higher prevalence of CAA in our study; the prevalence of CAA was higher in the 100+ subgroup when compared to the age group of 85-89 years (75% vs 62%). The increased prevalence of CAA in older age groups has indeed been reported by other studies (Masuda et al. 1988, Yamada et al. 2002). Another main reason for the higher CAA prevalence in our study could be our comprehensive sampling system which took into account the meningeal CAA, and our analysing six different brain areas. The meningeal CAA has been reported to be more prevalent (69.5%) than cortical CAA (59.3%) (Attems et al. 2007). In our study, the severity of CAA was significantly higher in the meningeal than in the cortical blood vessels (median 1.5% vs 0.3%). Without the meningeal deposition, as assessed in some previous population-based studies (Masuda et al. 1988, Pfeifer et al. 2002), the prevalence of purely parenchymal CAA was 59.3% in our study, in line with those previous studies. In addition, analysing the whole specimens in six brain regions increased the likelihood of observing the A β

deposits. In most previous studies, a lower number of brain regions have been analysed (Attems et al. 2011).

(3.) Although the prevalence of CAA was high in our study, in most cases, the severity of CAA was quite low. The median of CAA was 1% of the vessels, in accordance with previous studies (Yamada et al. 1987, Masuda et al. 1988).

(4.) The presence and severity of CAA vary by brain region (Attems et al. 2007). In this study, samples from six brain regions (frontal, parietal, temporal, occipital cortex, hippocampus and cerebellum) of each of 300 subjects were evaluated, which enabled us to examine various regions separately. In our study, CAA was most prevalent in the parietal lobe (57.8%) and least frequent in the hippocampus (39.0%) and cerebellum (31.4%). Thus, the topography of CAA resembles the distribution of plaque pathology described by Thal (Thal et al. 2002b). In this study, the severity of CAA was the highest in the frontal lobe (median 1.0%, range 0-77%) as previously noted in a population-based cohort study (Masuda et al. 1988).

(5.) CAA was more prevalent and severe in men. In our cohort, both the prevalence and severity of CAA were higher in men than in women. This may reflect just the smaller proportion of men in our very aged cohort. Nevertheless, our results are in line with those of previous studies, the males showing higher CAA scores than the females in the cortical regions, at least in AD cases (Shinohara et al. 2016). In previous population-based studies, there has been no evidence that the prevalence of CAA varies with gender (Xu et al. 2003, Keage et al. 2009), although somewhat more CAA has been detected in women in one previous study (28% vs 18.3%) (Masuda et al. 1988).

(6.) Neither the prevalence nor the severity of CAA was associated with age at death, as previously noted (Ringman et al. 2014). In our study, the prevalence was higher in the oldest (>100years) than the youngest (85-89 years) age group (75% and 62.7%, respectively), although the difference was not significant. This is in contrast to the results of our previous study (Tanskanen et al. 2005) focused on the cohort of 95+, in which the prevalence of CAA was 44%. It is, however, noteworthy that the 95+ cohort was analysed only with Congo red-stained samples without immunohistochemistry, which possibly hindered the observation of very scanty depositions of A β .

5.2 Frequency and severity of capillary amyloid β (II):

In this study, CAA was divided into two morphological categories, depending on the occurrence of capA β deposition, according to the study of Dietmar Thal, resulting in the categories of CAA-Type1 with capA β and CAA-Type2 without it (Thal et al. 2002a). According to my knowledge, this is the first population-based study of the topography and severity of capA β in several brain regions.

(1.) In this study, we noted capA β (CAA-Type1) in 86 subjects, each also having large vessel CAA. In total, 39% (86/221) of subjects with CAA also had capillary deposition. In the smaller hospital-based cohort reported on by Thal, the percentage of CAA cases with capA β deposition was exactly the same: 16 of 41 CAA cases (39%) (Thal et al. 2002a).

(2.) CapA β deposition seems to occur in the same brain regions as the general CAA (Thal et al. 2008b). We noted capA β most frequently in the occipital cortex 79/86, then in the hippocampus, temporal lobe, frontal and parietal lobes and cerebellum, following the topography of CAA as described in previous studies (Thal et al. 2008b). The CapA β deposition was also shown in the subiculum-CA1 region and the entorhinal cortex, in accordance with a previous study (Thal et al. 2008b). One third of the subjects with capA β had solely occipital capA β deposition, without capillary deposition in any other brain region. Severe capA β (grades 2-3, more than one affected capillary /HPF) deposition was observed in one third of the capA β cases, most frequently in the occipital, hippocampal and temporal lobes. In one fifth of the cases with capA β , the finding was simultaneously severe (> 1 /HPF, grade 2-3) and multiple (more than just one brain region).

(3.) The relationship between the development of general CAA and capA β deposition is still unclear. Some authors have proposed that the accumulation of the general CAA and capA β are at least partially separate processes because the correlation between the severity of general CAA and occurrence of capA β is absent (Thal et al. 2002a). On the other hand, many authors have noted that the severity of general CAA is associated with the presence of capillary deposition (Attems et al. 2004a, Richard et al. 2010). CAA of small arterioles has been considered to be the end stage of the most severe CAA (Olichney et al. 2000), representing an indicator of a high-grade CAA (Attems et al. 2004b).

However, the presence of capA β has been noticed to associate with CAA severity in some hospital-based studies (Attems et al. 2004a, Richard et al. 2010). In our population-based sample, subjects

with capA β (CAA-Type1) had a significantly higher percentage of large vessel CAA, than those without (CAA-Type2) (median 7.58% vs 1.33%), in line with other studies. The result was even clearer in subjects with severe capA β in multiple brain regions, the median of large vessel CAA (in all six brain regions) being 15.5% (with a mean as high as 24.8%, SD 21.1).

Despite these findings, we could not answer the question of whether capA β represents the end stage of large vessel CAA as previously thought (Olichney et al. 2000) or is a distinct entity (Thal et al. 2002a). It is interesting that in this study, the presence of capA β (CAA-Type1) was associated more strongly with the ADRP than general CAA.

(4.) Both the presence and severity of capA β (CAA-Type1) have been noted to associate with NFT (Braak stage) and NP (CERAD score) pathologies (Attems et al. 2004a, Attems et al. 2010). We confirm the association of capA β (CAA-Type1) with severe ADRP (Braak stages V-VI, CERAD F). In our study, capA β associated more strongly with the CERAD score than with the Braak stage ($p < 0.009$ and $p < 0.017$) in the multivariate analysis. Our result is in line with previous results depicting a stronger association with the NP pathology (Thal et al. 2002a, Richard et al. 2010). No association of a distinct CAA-Type with brain infarction or haemorrhage has been reported in previous studies (Thal et al. 2010), nor in our study. Furthermore, we found no significant association between the severe AD pathology and CAA-Type2.

(5.) CAA with capA β (CAA-Type1) has been shown to be associated more frequently with the AD-related genetic risk locus *APOE* $\epsilon 4$, than has CAA without capA β (CAA-Type2) (Thal et al. 2002a, Richard et al. 2010). In previous studies, subjects with at least one *APOE* $\epsilon 4$ allele have been demonstrated to have higher capA β scores (Richard et al. 2010). This is in agreement with our result, as we detected a significant association between CAA-Type1 and the *APOE* $\epsilon 4$ allele ($p < 0.001$).

In our study, two individuals were homozygous for $\epsilon 4$ (2/278, 0.7%), both representing CAA-Type1. That is in line with previous studies, subjects homozygous for the $\epsilon 4$ allele having the strongest association with capA β (Richard et al. 2010). Furthermore, CAA-Type2, in contrast to CAA-Type1 or controls, has frequently been shown to be associated with the *APOE* $\epsilon 2$ allele (Thal et al. 2002a). We did not find any association between the CAA-Type2 and the $\epsilon 2$ allele.

(6.) Dementia: In our study, dementia was clearly more common in subjects with capA β than without (CAA-Type1: 83.7%, CAA-Type2: 62.2% and non-CAA: 49.3%). That was in accordance with previous studies, which have proven CAA-Type1 to be associated with dementia (Thal et al. 2008b)

and AD (Attems et al. 2010). On the other hand, in our study, capA β (CAA-Type1) was detected only in 36.9% of the demented and 14 (16.3%) of non-demented subjects had capA β (CAA-Type1). There are no other population-based studies on the prevalence of capA β in the demented.

In our study, the hippocampal finding of capA β was quite uncommon and mostly mild. CapA β deposition was observed in 48 subjects in the hippocampus, of which 10 had capA β at the cornu ammonis (CA4-CA1 regions), in addition to other hippocampal structures. In subjects expressing capA β in the CA4-CA1 regions, the median of large vessel CAA in all six brain regions was very high (17.25%) and all these subjects were demented (10/10). In addition, nearly all subjects with only slight (grade 1) hippocampal capA β deposition at the subiculum were demented (6/7), without capA β in any other brain region. These results can be seen to highlight the importance of hippocampal pathology in dementia, even though this aspect needs to be studied more carefully in a larger cohort.

All individuals (14/14) with multiple-capA β (severe capA β at five or six brain regions) were also all demented, each had the CERAD score F (100% vs 33.7% in CAA-Type1) and a higher median value of general CAA (15.5% vs 7.58% in CAA-Type1). Those few cases with multiple-capA β did not show any association with the severe Braak stage, which is in contrast to a previous study, where the severity of A β 42 deposits at capillaries significantly correlated with the Braak stage (Attems et al. 2004b).

5.3 Neuropathological correlates of dementia (III)

(1.) In elderly people, regardless of the cognitive level, all kinds of neuropathological changes are common findings. In our study on 300 subjects, all except one (99.7%) had at least one type of neuropathological finding (Braak, CERAD, LB-related, and CAA, infarct or haemorrhage). Vascular findings were very common, as CAA was found in 70%, micro-haemorrhages in 62% and brain infarcts in 60% of the subjects. These figures are in line with the previous population-based studies on the elderly: For example, the Honolulu-Asia study (HAAS study) detected a 99% occurrence of the AD-type neuropathology and a 78% occurrence of the vascular-type neuropathology (Launer et al. 2008).

(2.) In our study, three variables were associated independently with dementia: the severe NFT pathology (Braak stage V-VI), the diffuse neocortical type of LB-related pathology, small (2-15mm) cortical anterior infarcts.

The severe Braak stage (V-VI) was the strongest contributor of dementia in our study, as has been observed in other population-based studies, such as the CFAS, Baltimore and CC75C studies (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001, Troncoso et al. 2008, Brayne et al. 2009).

In our study, the neocortical LB-related pathology in particular was associated significantly with dementia (OR 4.78; 95% CI 1.94-11.78), while the LB-related pathology in the brainstem and limbic regions was not associated with dementia. The result was parallel with previous work by Schneider et al. (Schneider et al. 2007). In many studies, such as CFAS and Rush Memory, the LB-related pathology has been observed to be equally common in demented and non-demented individuals (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001, Schneider et al. 2007), and the LB-related pathology has been observed to co-exist with the AD pathology (Wakisaka et al. 2003). In our study, the combination of NFT and neocortical LB-related pathologies produced the highest risk.

Vascular changes in the brain parenchyma have been observed to increase the overall risk of clinical dementia (Snowdon et al. 1997). That finding has been confirmed in the population-based HAAS study (Petrovitch et al. 2005). The elderly demented AD patients in particular have been observed to have concomitant vascular changes (Snowdon et al. 1997, Massoud et al. 1999). Vascular changes are also believed to affect the onset and progression to AD (Zlokovic et al. 2011, Viswanathan et al. 2011, Kalaria et al. 2000).

Population- or community-based neuropathological studies have repeatedly perceived multiple cortical small infarcts or micro-infarcts as significant, independent causes of dementia (White et al. 2002, Schneider et al. 2004, Sonnen et al. 2007, Troncoso et al. 2008, Brayne et al. 2009). An independent association of small (2-15mm) cortical anterior infarcts with dementia was confirmed in this study.

(3.) Our notion of severe frontal CAA associating with dementia quite strongly (borderline association with dementia in multivariate analysis $p = 0.057$) is in line with the previous population-based CFAS study (Neuropathology Group. Medical Research Council Cognitive Function and Aging Study 2001), in which an association between severe CAA and dementia was more prevalent (73.0% vs 49.1%) and significantly more severe (6% vs 2%) among the demented than the non-demented participants, such also being in line with previously reported findings in hospital-based cohorts (Attems et al. 2007) and in the population-based MRC CFAS (Matthews et al. 2009) and HAAS studies (Pfeifer et al. 2002).

Overall CAA has been detected in over 80% of AD patients (Esiri, Wilcock 1986, Yamada et al. 1987, Ellis et al. 1996, Attems et al. 2007) and has been suggested to have an essential role in the pathogenesis of AD (Nicoll et al. 2004). As a result, CAA has been elaborated here as a part of the AD-type neuropathology (Vinters et al. 1992, Vinters et al. 2001) as in the guidelines for Alzheimer's disease (Hyman et al. 2012) and not as a part of vascular pathology.

(4.) In this study, the different types of neuropathologies formed three separate clusters in relation to each other. (1) AD-type and LB-related pathology and CAA, (2) Macroscopic infarcts of >2mm, (3) cortical micro-infarcts and micro-haemorrhages. Even though many elderly individuals have been observed to have both the AD-type and vascular neuropathology, how vascular pathologies influence the clinical outcome of the AD-related pathology (additive or synergistic effect) is not clear (Launer et al. 2008, Troncoso et al. 2008). The AD-type pathology and infarcts are the most common combination in demented individuals (Schneider et al. 2007). About 30% of the AD subjects seem to have a comorbid cerebral infarction (Olichney et al. 1997). However, not all studies have found any statistical association between the AD-type lesions and vascular lesions (Launer et al. 2008). In addition to this, the AD and vascular types of pathology have been supposed to influence the dementia risk in different ways (CFAS 2001). Our factor analysis results support this view.

(5.) Multipathology, (co-occurrence of two or more of the independent pathologies) almost doubled the risk of dementia in our study. One third of the demented had two or more separate neuropathological findings concomitantly, and their odds of dementia were almost two times higher than for those with only one of the pathologies (OR 10.07 vs 5.41). This is in the line with the other studies, where the higher number of pathologies was discovered to be associated with a greater severity of dementia (Kawas et al. 2015). A threefold increase in the odds of dementia has been reported when more than one neuropathological variable is present (Schneider et al. 2007). In the 90+ study, three or more pathologies simultaneously raised the occurrence of dementia to 95% (Kawas et al. 2015).

5.4 Alzheimer's disease-type genetic risk loci (IV)

In addition to FAD, sporadic AD has a clear inherited component. The *APOE* $\epsilon 4$ allele is known to be an unequivocal risk factor for AD. In addition to its association with clinical AD, the *APOE* $\epsilon 4$ strongly associates with neuropathological findings of AD (Saunders et al. 1993, Shulman et al.

2013, Beecham et al. 2014). In this study, we confirmed the strong association between different forms of the ADRP (CERAD score, Braak stage, CAA, capA β) and *APOE* $\epsilon 4$, as we have documented before in our own previously published data (Polvikoski et al. 1995, Peuralinna et al. 2011).

APOE $\epsilon 4$ has been observed to influence associations between AD and other loci (Wijsman et al. 2011). Therefore, in this study we performed association analyses of the AD risk loci in two ways, with and without the *APOE* $\epsilon 4$ adjustment. The *APOE* adjustment did not remarkably alter the associations between the neuropathological features in most loci.

(1.) In this study, we focused on the associations of the recently reported, near thirty GWAS-based AD loci (Table 8), some of them having already been investigated previously by candidate gene and linkage analysis (other than *APOE* $\epsilon 4$). Initially, we used the SNP array data of 44 variants of 29 loci for 327 521 variants from 512 participants (Illumina, GWAS data generated previously (Peuralinna et al. 2015) by Infinium Human370 BeadChips (Illumina, San Diego CA)) to seek associations between these loci and different neuropathological variables. Unfortunately, in the SNP array there were no variants of loci *EXOC3L2*, *HLA-DRB1* and *TREM2*. However, we performed an imputation (estimated the frequencies of a large number of genotypes, based on the whole genome sequencing data available for approximately half of the population). The imputed data covered these areas. The data imputation also greatly increased the number of variants we could assess in other loci.

Table 8. Results of the binary logistic/linear regression analysis of the severe AD histopathology and risk loci for 341 markers in SNP array data and in the imputed data of 6 038 variants remained in 29 loci.

GENE	Chr	capA β SNP	Imputed	CAA SNP	imputed	CERAD SNP	imputed	Braak SNP	imputed
ABCA7	19			+	+				+
ABCG1	21				+	+	+	+	+
APP	21	+	+		+		+	+	+
BIN1	2	+	+		+		+		
CASS4	20				+				
CD2AP	6				+				+
CD33	19								

CELF1	11								
CLU	8				+				
CR1	1		+	+	+				+
EXOCC3L2	19								
EPHA1	7								
FERMT2	14	+	+	+	+	+	+		
GAB2	11				+		+		+
GALNT7	4	+	+	+	+			+	+
HLADRB1	6		+		+				
HLADRB5	6								
INPP5D	2								
MEF2C	5		+			+	+		+
MS4A	11	+	+		+	+	+		+
NME8	7	+	+	+	+		+		+
PICALM	11		+		+	+	+		
PTK2B	8	+	+			+	+	+	+
Region chr9	9		+		+		+		+
SLC24A4	14		+	+	+	+	+	+	+
SORL1	11		+	+	+	+	+	+	+
TREM2	6		+						
TRIP4	15				+			+	+
ZCWPW1	7			+	+				

Adjusted for age of death, gender, with or without carrier status of the *APOE ε4* allele. All the markers with $p < 0.05$ are shown. N= the number of markers at the locus (in total, 341 markers in the SNP array data, and in the imputed data of 6 038 variants mapped into 29 loci).

AD risk loci were compared with tau pathology (Braak IV-VI vs 0-II), A β plaque pathology (CERAD M-F vs 0-S), and presence of capA β (yes or no) by logistic regression analysis. CAA was analysed as a continuous variable by linear regression.

Of the 512 samples, 487 passed the quality control criteria. In the SNP array data, there were 341 variants at 26 candidate loci and in the imputed dataset, 6 038 variants in 29 loci. All the 29 candidate loci were covered in either the original SNP array or imputed datasets. The size of the neuropathologically and genetically examined subpopulations was 256. Our material thus covers the loci of interest well.

24 of the 29 examined AD risk loci were associated with one or more ADRP (CERAD, Braak, CAA, capA β). The result was in line with the previous neuropathological studies (Beecham et al. 2014). In our SNP array data, none of the 29 loci associated with all the neuropathological variables, but in the imputed data, five loci, *APP*, Chr9 region, NME/NM23 family member 8 (*NME8*), Solute Carrier family 24, member 4 (*SLC24A4*) and *SORL1* were associated with all the neuropathological variables (CERAD, Braak, CAA and CapA β). On the other hand, in the SNP array data, nine loci (Cas scaffolding protein family member 4 (*CASS4*), *CD2AP*, *CD33*, *CELF1*, *CLU*, *Epherin receptor A1* (*EPHA1*), *GAB2*, Major histocompatibility complex, class II, DR beta 5 (*HLADRB5*) and *INPP5D*) and in the imputed data, five loci (*CD33*, *CUG RNA-binding protein and embryonal lethal abnormal vision-type RNA-binding protein 3-like factor1* (*CELF1*), *EPHA1*, *HLADRB5* and *INPP5D*) showed no association with any neuropathological feature (Table 8).

(2.) In the previous GWAS-based studies containing neuropathological data, some AD risk loci had been observed to associate either with the NP or NFT pathology or both (Table 5) (Beecham et al. 2014). Both the NPs and NFTs have been noticed to associate with the following loci: *ABCA7*, *BIN1*, *CASS4*, Myocyte Enhancer Factor 2C (*MEF2C*), and *PICALM* (Beecham et al. 2014). In our study, the following loci in the SNP data associated both with the NP and NFT pathology: *ABCG1*, Membrane-Spanning 4-domains, subfamily A (*MS4A*), Protein Tyrosine Kinase 2 beta (*PTK2B*), Solute Carrier family 24, member 4 (*SLC24A4*) and, *SORL1*. The associations with both NP and NFT pathology were also detected in the imputed data with *APP*, Growth factor receptor-bound protein 2-associated binding protein 2 (*GAB2*), *MEF2*, *NME8*, region 9 (Table 8.).

A specific association of NPs has also been found with loci *ABCG1*, GalNAc transferase 7 (*GALNT7*), *MS4A6A* and, *CD33*. In a previous work by Beecham and collaborators, no association with *CR1* loci and NPs was detected (Beecham et al. 2014), but in the report by Shulman et al., *CR1* was associated with the NP burden as were loci *ABCA7* and *CD2AP* (Shulman et al. 2013). We

confirmed the association of *ABCG1*, *MEF2*, *MS4A* and *PICALM*, and in addition we also observed the associations of loci *APP*, *BIN1*, Fermitin family member 2 (*FERMT2*), *GAB2*, *NME8*, *PTK2B*, region chr9, *SLC24A4* and *SORL1* with a severe NP burden.

The strongest association in our study was found both in the SNP array data and imputed data between the CERAD score and the *MEF2C* locus (rs700588), ($p = 0.0002122$, OR 2.67, 95% CI 1.59-4.49 SNP adjusted with *APOEε4* and without $p = 0.0003895$, OR 2.40, 95% CI 1.48- 3.88). The *MEF2C* gene (myocyte enhancer factor 2C) influences the immune system and is thought to have a role in B cell proliferation. In addition, *MEF2C* has been proposed to affect the development of the muscle and nervous system (Flavell et al. 2006), to regulate the synapse number in the hippocampus (Rashid et al. 2014) and to reduce dendritic spines impairing memory formation (Cole et al. 2012). *MEF2C* has also been thought to regulate microglia proliferation (Zhang et al. 2015), to be upregulated in activated vascular smooth muscle cells (Firulli et al. 1996) and to modulate the APP proteolytic process affecting A β production (Camargo et al. 2015).

(3.) We observed six loci (*ABCG1*, *APP*, *GALNT7*, *PTK2B*, *SLC24A4*, *SORL1*) to be associated with a high Braak stage in the SNP array data and 15 (the above and *ABCA7*, *CD2AP*, *CR1*, *GAB2*, *MEF2C*, *MS4A*, *NME8*, region chr9, *TRIP4*) in the imputed data (Table 8). We confirmed the previous finding with the *ABCA7*, *MEF2C* and *SORL1* loci, but we did not find the association with loci *BIN1*, *CASS4*, *CLU*, *SORL1*, *ZCWPW1* or *PICALM*, which were reported by previous studies (Beecham et al. 2014). In our study, the *GAB2* locus (rs2512518) had the strongest association ($p = 0.004372$, OR=0.31, 95% CI 0.14-0.69). *GAB2* is an intracellular protein which is believed to influence cell growth, differentiation and apoptosis (Sarmay et al. 2006). *GAB2* could have interactions with *APP* and *PSEN* and is possibly involved in the AD pathogenesis (Nizzari et al. 2007, Reiman et al. 2007, Russo et al. 2005). Overall, in our work, the associations with the Braak stage were weaker than those with the CERAD score.

(4.) In previous GWAS-based studies containing neuropathological data, no associations with CAA have been detected, except for the *APOE* locus (Beecham et al. 2014). One explanation for this is that only the presence or absence of CAA has been determined in most neuropathological studies and no attention has been paid to the severity of CAA (Beecham et al. 2014). Nevertheless, it is well known that mild CAA is very prevalent in the elderly and does not associate with AD. Severe CAA has shown to be associated with AD and could have revealed some associated risk loci in the previous study if GWAS had been focused on the severe CAA cases.

Seven and twenty loci were associated with the severity of CAA in the SNP array data and the imputed data, respectively (Table 8). *CASS4*, *CLU*, and Zing-finger, CW type with PWWp domain 1 (*ZCWPW1*) were associated only with the severity of CAA and no other neuropathological variable. The strongest association with the CAA severity (apart from *APOE* ϵ 4) was with *CR1* (rs65087, $p=0.004934$, beta 2.52, 95%CI 0.78- 4.26 without the *APOE* ϵ 4 adjustment). This was confirmed in our imputed data with rs185310342 at the *CR1* locus ($p=7.17E-07$, Beta 14.4, 95% CI 8.88-20 without the *APOE* ϵ 4 adjustment). These findings were in line with the results of the Longitudinal Religious Orders Study, where *CR1* was found to be associated with the CAA burden in a candidate gene analysis (Biffi et al. 2012). *CR1* is a large glycoprotein containing many polymorphisms. *CR1* has been thought to regulate complement activation and to be involved in the clearance of soluble A β particles (Fallman et al. 1993, Tas et al. 1999).

(5.) No previous GWAS study has been performed using capA β as the phenotype. In this study, seven loci in the SNP array data (*APP*, *BIN1*, *MS4A*, *PTK2b*, *GALANT7*, *NME8* and *FERMT2*) and 15 loci in imputed data associated with capA β (Table 8). Our results provide information on the partly shared and partly distinct genetic backgrounds of different AD-related neuropathological features and general CAA.

In the SNP array data, the most significant association was found with *APP* (rs1783016, $p=0.005933$ OR 2.01, 95% CI 1.22- 3.30 with *APOE* ϵ 4 adjustment). Mutations in *APP* lead to the formation of neurotoxic oligomers of A β (Benilova et al. 2012) and, according to the amyloid cascade hypothesis, then to the accumulation of hyper-phosphorylated tau, synaptic loss and cognitive decline.

With the imputed data, the strongest association with capA β was with rs66962766 in the *HLA-DRB1* locus ($p=0.002594$, OR 0.54, 95% CI 0.37-0.81). *HLA-DRB1* (Human leucocyte antigen-class II, DR beta 1/5) is part of an extracellular protein, involved in the immune system, inflammation, complement cascade etc. (Downs-Kelly et al. 2007). *HLA-DR* positive activated microglia have been observed in Parkinson's disease and a similar effect has been postulated in AD, too (Zhang et al. 2015). In this study, *HLA-DRB1* associated with both CAA and capA β , but not with other pathologies.

TREM2, a locus also having a role in the immune response, was associated only with capA β . This is an interesting finding, suggesting a partially distinct risk loci profile for CAA and capA β . The *TREM2* variants have been observed to increase the risk of AD at an earlier age (Guerreiro et al.

2013, Jonsson et al. 2013) and greater hippocampal atrophy (Rajagopalan et al. 2013). Even though less prevalent than *APOE* $\epsilon 4$, *TREM2* has been identified as a locus with a similar effect size as *APOE* $\epsilon 4$ for AD (Guerreiro et al. 2013, Jonsson et al. 2013).

CONCLUSIONS

The aim of the study was to clarify the prevalence of vascular and neurodegenerative pathologies and their relation to dementia in a very elderly population (Vantaa85+ Study). Furthermore, our purpose was to systematically study the prevalence, topography and severity of general CAA and capA β in several brain regions, and to analyse the genetic background of the different neuropathological features of AD.

(I) In this population-based study, CAA was highly prevalent among the elderly, but in most cases mild in severity. CAA was most prevalent in the parietal and most severe in the frontal lobe.

(II) We divided CAA into two distinct types on the basis of the occurrence of capA β according to Thal (Thal, et al. 2002a). CAA with capA β (CAA-Type1) associated strongly with severe AD-related pathologies, severe CAA and the carrier status of *APOE* $\epsilon 4$. The result highlights the role of capA β in the neuropathological diagnosis of AD.

(III) We demonstrated that multipathology commonly underlies dementia, particularly in the oldest old. At the population level, AD-type neurodegenerative processes play the most prominent role in cognitive decline. In this population-based study we discovered three independent contributors to dementia: accumulation of the AD-type tau-pathology (Braak stage V-VI), neocortical LB-related pathology, and cortical anterior 2-15 mm infarcts. Severe CAA in the frontal lobe was nearly significantly associated with dementia. 31.3% of the demented had at least two of these pathologies and the co-occurrence of more than two of these independent pathologies almost doubled the risk of dementia.

(IV) In addition to confirming the *APOE* $\epsilon 4$ association with all the AD-type neuropathologies, we found an association of 24 out of 29 previously identified GWAS-based AD risk loci with one or more of the histopathological ADRP variables (CERAD score, Braak stage, CAA and capA β). The genetic risk loci profiles of CAA and capA β have not been studied in population-based settings before, and we discovered them to be partially distinct compared to the other neuropathological features of AD.

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ELECTRONIC RESOURCES

EuroCoDe-Study (European Collaboraton on Dementia 2013, ec.europa.eu/health)

National Institute of Health and Welfare, Finland (THL)

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